North East and North Cumbria Clinical Networks

North East and North Cumbria Local Maternity System

TITLE	**North East and North Cumbria (NENC) Epilepsy in Pregnancy Regional Guideline**
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1. Introduction

Epilepsy is the one of the most common neurological conditions in pregnancy, with a prevalence of 0.5–1%. 23% of people with epilepsy are women of childbearing age. Although the majority of mothers with epilepsy have straightforward pregnancies and healthy babies, there is an increased risk to mothers and babies and women should therefore be cared for by a multidisciplinary specialist team.

The mortality rate is known to be two to three-fold higher in people with epilepsy than in those without the diagnosis. This is further increased in pregnancy, where the rate is increased ten-fold in women with epilepsy (WWE) compared to those without the condition. Twenty-two maternal deaths that occurred between 2016-2018 were attributed to epilepsy (MBRRACE-UK 2020 report). This compares to thirteen women in 2013-15. Of particular concern is that eighteen women died from SUDEP (Sudden Unexpected Death in Epilepsy) in 2016-18, more than a doubling of the rate of SUDEP in the previous report. The majority of women had uncontrolled epilepsy pre-pregnancy with very few having had documented pre-pregnancy counselling, and fewer than half having had specialist review during pregnancy. Lamotrigine, levels of which fall significantly in pregnancy, was the drug most used by the women that died.

The risk of major congenital malformation in the fetus is increased in WWE on anti-epileptic drugs (AEDs). Exposure to valproate and potentially other AEDs may also have an adverse effect on the neurodevelopment of the newborn in the long term.

2. Purpose

This guideline is to provide evidence-based information and to promote and ensure good quality maternity care for women with epilepsy across the North East and North Cumbria Maternity Clinical Network for all healthcare professionals involved in the antenatal, intrapartum and postpartum care of women diagnosed with epilepsy.

The aim of management is to remain seizure free pre-conceptually and during pregnancy by using the lowest effect dose of an anti-epileptic drug (AEDs) and avoiding polypharmacy (more than one AED) of AEDs.

3. Diagnosis of epilepsy

The diagnosis of epilepsy should be made by a neurologist (see Appendix 1).

4. Pre-pregnancy counselling and management

4.1 Information regarding contraception and pregnancy should be given to women and girls in advance of sexual activity. This information should also, where appropriate, be given

to people closely involved with the care of these patients. Medical staff should be aware of individual AED drug interactions in relation to contraception and be able to advise patients accordingly.

4.2 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 peri-conception Period (whilst trying for a baby and in very early pregnancy).

Clinicians should consult the findings of the epilepsy medicines in pregnancy review (MHRA) when considering prescribing AEDs in women. They should be aware that lamotrigine and levetiracetam are not associated with an increased risk of birth defects compared with the general population.

Women should be informed that the risk of congenital abnormalities in the fetus is dependent on the type, number and dose of AED. The risk is highest with use of AEDs in the first trimester and with polytherapy. The most common major congenital malformations associated with AEDs are neural tube defects, congenital heart disorders, urinary tract and skeletal abnormalities and cleft palate. Valproate is associated with neural tube defects (NTDs), facial cleft and hypospadias; phenobarbital and phenytoin with cardiac malformations; and phenytoin and carbamazepine with cleft palate.

Valproate should be avoided in girls and women of childbearing potential; unborn babies exposed to valproate during pregnancy are at high risk of congenital malformation (11%) and very high risk (40%) of neurodevelopment disability such as lower intelligence and autistic spectrum disorder. WWE and their partners should be informed about the very high risk of in utero exposure to valproate on the long-term neurodevelopment of the newborn. MRHA advice also states:

- Valproate must no longer be used in any woman or girl able to have children, unless she has a 'Valproate Pregnancy Prevention Programme' in place which is reviewed on an annual basis by an epilepsy specialist.
- Women currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so. Any woman who thinks they are pregnant while on valproate should be advised to talk to a neurologist urgently.
- See MHRA links below for information, advice, and annual risk acknowledgement forms.
    - Valproate: reminder of current Pregnancy Prevention Programme requirements; information on new safety measures to be introduced in the coming months - GOV.UK (www.gov.uk)
    - https://www.gov.uk/guidance/valproate-use-by-women-and-girls#history

A safety review by the MHRA of the use of topiramate in pregnancy in July 2022, highlighted potential risks associated with topiramate use in pregnancy including an increased risk of teratogenicity including neurodevelopmental disability. Further guidance is expected to be issued, in the interim, topiramate use should be carefully reviewed ahead of planned pregnancy or early on during pregnancy if the patient has an unplanned pregnancy.

The safety evidence is currently insufficient for the newer AEDs (including zonisamide, brivaracetam, lacosamide, esclicarbazapine, gabapentin) in pregnancy.

4.3. The majority of women (66.6%) do not experience a seizure in pregnancy. The seizure-free duration is the most important factor in assessing the risk of seizure deterioration. In women who are seizure free for at least 9 months to 1 year prior to pregnancy, 74–92% continue to be seizure free in pregnancy. In those with generalised tonic-clonic seizures the fetus is at relatively higher risk of harm during a seizure, but the absolute risk remains low, and the level of risk depends on seizure frequency.

Women with poor seizure control should be advised against pregnancy and be referred to a specialist neurologist to achieve optimum control prior to pregnancy.

There is no evidence that focal, absence, myoclonic seizures or dissociative (non-epileptic) seizures affect the pregnancy or developing fetus adversely unless they cause a fall and subsequent injury.

Women should be advised of the risk of sudden unexplained death should they decide to discontinue all AEDs. Counselling of the withdrawal of AEDs should include a discussion of the recommendations by the DVLA.

WWE should be advised to have a healthy balanced diet preconception, during pregnancy and whilst breastfeeding. Information is available on diet and nutrition from the Epilepsy Society

Vitamin D supplementation (10mg) is also advised and is particularly important in WWE as evidence suggests a link between low levels and AED's affecting seizure control. People eligible for the Healthy Start Scheme are entitled to free mother and infant vitamins - Getting vitamins – Get help to buy food and milk (Healthy Start)

WWE should be prescribed folic acid 5mg per day 12 weeks prior to conception. This should be continued during the first trimester.

4.4 Consider genetic counselling if one partner has epilepsy, especially if this is idiopathic and there is a positive family history.

5. Antenatal management

5.1 Pregnant WWE should have access to regular planned antenatal care with a designated epilepsy care team including a named obstetrician, neurologist and epilepsy specialist nurse, all with an interest in epilepsy and pregnancy.

All pregnant WWE should be seen jointly by an obstetrician and an epilepsy specialist nurse, both with an interest in epilepsy and pregnancy for an early booking assessment. This should be as early as possible in pregnancy (before the dating scan if seizures within the previous 6 months). A plan should be made for place of antenatal care/birth (see Appendix 2). A neurologist should be available for advice on management.

Women with complex epilepsy (see Appendix 2) should be seen jointly by an obstetrician, a neurologist and an epilepsy specialist nurse, all with an interest in epilepsy and pregnancy for an early assessment (before the dating scan) and to plan place of antenatal care/birth.

Maternity units without a combined antenatal clinic (obstetrician and epilepsy specialist nurse and access to a neurologist locally) should arrange for the woman to be referred to the Maternal Medicine Centre so that her antenatal care and place of birth can be discussed at a Maternal Medicine MDT meeting early in pregnancy. Women are referred by the maternal medicine team in their local maternity unit (referrals can be made through Badgernet or by emailing a referral form to nuth.matmedteam@nhs.net)

WWE taking AEDs who become unexpectedly pregnant should be able to discuss therapy with a neurologist on an urgent basis.

Women with a history of epilepsy but who are no longer considered having a predisposition to unprovoked seizures (seizure free for 10 years with 5 years off anti-seizure medication) can be managed as low-risk women in pregnancy.

5.2 Women should be given advice regarding coping with morning sickness and avoiding seizure triggers (lack of sleep and missed medication) and advised of the dangers of bathing during pregnancy. Women should be advised to bathe only in shallow water with someone else in the house or alternatively to shower.

Women should be reassured that most women will have a healthy pregnancy but there is an increased risk of complications during pregnancy and labour and increased need for induction of labour and caesarean section if their epilepsy is poorly controlled.

Women should be reassured that an increase of seizure activity is unlikely in pregnancy and in the first few months after delivery. The risk of tonic-clonic seizure during labour and within 24 hours of delivery is low (1-4%).

WWE should be reassured that most women will have an uncomplicated labour and delivery. For WWE with a significant deterioration of seizures, timing and mode of delivery should be discussed with the multidisciplinary team.

Women should be informed that the risk of injury to the fetus during a maternal seizure is low. Precipitants for seizures can be pain, stress and sleep deprivation, dehydration and non-compliance with medication. It is important to explain this to women so that they are aware of these precipitants and can take measures to prevent seizures.

All pregnant women should be given information regarding status epilepticus and sudden unexplained death in epilepsy should they decide to discontinue AEDs.

5.3 WWE should be provided with information about the UK Epilepsy in Pregnancy Register. Consent should be sent to UK Epilepsy and Pregnancy Register, Dr J I Morrow, Department of Neurology, Royal Victoria Hospital, Governor Road, Belfast BT12 6BA.

5.4 An early pregnancy scan (12-14 weeks) should be used as an opportunity to screen for structural abnormalities. The fetal anomaly scan (18+0 – 20+6 weeks of gestation) can identify major cardiac anomalies and NTDs.

Recommend serial growth scans in WWE from 32 weeks. WWE on AEDs have been shown to have an increased risk of fetal growth restriction.

5.5 Measurement of blood levels of lamotrigine during pregnancy is currently recommended as lamotrigine levels lower during pregnancy due to changes in metabolism. A trough level should be measured at booking, 20 weeks, 24 weeks, 28 weeks, 32 weeks, and 36 weeks. If lamotrigine dose is adjusted during the pregnancy due to lowering lamotrigine levels, a plan should be in place for post-natal reduction in lamotrigine dose within the 2 weeks post-partum to minimise the risk of toxicity after delivery. This should be managed by the neurology team only.

Routine measurement of blood levels of other AEDs is not currently recommended.

6. Intrapartum care

6.1 WWE should deliver in a consultant led unit. They should have one-to-one midwifery care and should not be left alone. Home birth and delivery in the pool is not advised.

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

6.2 AEDs should be continued during labour; women should be informed that the risk of seizures during labour is low but 1-2% of women with epilepsy may experience a seizure during labour and 1-2% within the 24 hours following delivery.

Use of antenatal corticosteroids in pregnant women with epilepsy is the same as that of pregnant women without epilepsy.

Adequate analgesia and appropriate care in labour should be provided to minimise risk factors for seizure such as insomnia, stress and dehydration. Avoid pethidine which is metabolized to the epileptogenic norpethidine.

6.3 Seizures in labour should be terminated as soon as possible to avoid maternal and fetal hypoxia.

Terminate seizure with IV lorazepam (0.1mg/kg (usually a 4mg bolus, with a further bolus 10-20 minutes later). Diazepam 5-10 mg intravenous is an alternative. For women with difficult venous access consider lorazepam 4mg IM or diazepam 10mg PR. If there is concern that the seizure could be due to eclampsia, then also treat with magnesium sulphate as per protocol.

Delivery should be expedited following a seizure during labour. Repeated seizures in labour put the fetus at risk of hypoxia and constitute an indication for early recourse to Caesarean section under general anaesthetic.

Any woman having a seizure during labour must be closely observed for the next 72 hours and all women with epilepsy should remain in hospital for 24 hours following delivery for observation.

Inform neonatal team, as there is a risk of neonatal withdrawal with maternal use of benzodiazepines.

7. Postnatal management

7.1 WWE and caregivers should be made aware that although the overall chance of seizures during and immediately after delivery is low, it is relatively higher in the postnatal period than during pregnancy. WWE should 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.

7.2 If the AED dose was increased in pregnancy, it should be reviewed within 10 days of delivery to avoid postpartum toxicity. An antenatal plan should have been made for any adjustment to medication in the postnatal period.

7.3 Breastfeeding should be encouraged in women on AEDs. Based on current evidence the risk of adverse cognitive outcomes is not increased in children exposed to AEDs (lamotrigine, levetiracetam, phenytoin and carbamazepine monotherapy) through breast milk.

With regular use of longer acting benzodiazepines e.g., clonazepam and clobazam, there is a risk of accumulation in the baby (infrequent doses do not carry this same risk) and the baby should be monitored after birth. This is particularly important in premature babies. Contact the neonatal team if any concerns.

7.4 All babies born to WWE taking AEDs should be offered 1 mg of intramuscular vitamin K to prevent haemorrhagic disease of the new-born (HDN).

7.5 Women should be given safety advice with respect to caring for the baby after delivery. The leaflet may be obtained from the British Epilepsy Association (www.epilepsy.org.uk)

8. Contraception

8.1 WWE should be offered contraception to avoid unplanned pregnancy. This discussion should ideally take place in the antenatal period, but if not, there should be a discussion before discharge from the postnatal ward.

8.2 Epilepsy itself is not a contraindication to any type of contraception (UKMEC1) however many of the medications used to treat epilepsy are not suitable for use with some hormonal contraception.

8.3 Copper and Levonogestrel IUDs and Depo-Provera should be promoted as reliable methods of contraception. They have no drug interactions and can be used in women on any AEDs.

8.4 Women taking enzyme-inducing AEDs including lamotrigine are not suitable for combined hormonal contraception, the progesterone only pill or the progesterone implant. For these methods of contraception please refer to the BNF interactions section to decide on suitability. Further information is available at: https://www.fsrh.org/standards-and-guidance/documents/ceu-clinical-guidance-drug-interactions-with-hormonal/

9. References

- Royal College of Obstetricians & Gynaecologists Green-top Guideline No.68: Epilepsy in Pregnancy. June 2016
- NICE Diagnosis and management of the epilepsies in adults and children in primary and secondary care: Clinical Guideline 137, 2012
- MBRRACE – UK: Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ, editors, on behalf of MBRRACE-UK. *Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland*

  Confidential Enquiries into Maternal Deaths and Morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2014.
- Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. CEU Statement (January 2010) Antiepileptic Drugs and Contraception
- MHRA Regulatory Agency. Valproate and neurodevelopmental disorders: new alert asking for patient review and further consideration of risk minimisation measures. Vol 10. Issue 9, April 2017

Appendix 1

Clinical presentation of seizures and their effect on the mother and baby

Common types of epilepsy/seizures	Clinical presentation	Effect 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 warning. Associated with variable period of fetal hypoxia.[18] This seizure type is associated with the highest risk of SUDEP.
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. May impair consciousness.	Impairment of consciousness increases risk of injury such as long bone fracture, dental or head injury, electrocution or burns than if consciousness is retained (an epileptic aura only). They can be associated with a variable period of hypoxia and risk of SUDEP.
Juvenile myoclonic epilepsy (JME)	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 awakening, or when tired. The sudden jerks may lead to falls or to dropping of objects including the baby.
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 modest. Worsening absence seizures places the women at high risk of tonic-clonic seizures.

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Referral Pathways for Women with Epilepsy (WWE)