Guideline for the management of women with epilepsy in pregnancy

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Key Amendments

Date	Amendments	Approved by

Introduction

Epilepsy is a common medical condition complicating pregnancy with an incidence of 6:1000 pregnancies. It is associated with an increased risk of injury and even death. The MBRRACE report (Saving Lives 2015) states that there were 7 deaths from epilepsy in 2011-13.The number of deaths due to epilepsy was higher in 2006-8 (14women died due to epilepsy in that triennium)compared to 2011-13.

Epilepsy impacts on many aspects of life and is still surrounded by stigma and prejudice.

Women with epilepsy should be informed that although they are likely to have healthy pregnancies, their risk of complications during pregnancy and labour is higher than that for non epileptic women.

There is exposure to antiepileptic drugs (AEDs) in approximately 0.3–0.6% of pregnancies. Women with epilepsy who are on anti-epileptic drugs (AEDs) have a three fold increased risk of congenital abnormalities.

Classification of seizure type

- Primary generalised epilepsy:
  - *Absences* (Brief pauses e.g. where stop talking for 10 sec and then carry on where left off)
  - *Myoclonic jerks* (e.g. thrown suddenly to the ground)
  - *Tonic-clonic* (Classic “grand mal” : sudden onset with loss of consciousness, limbs stiffen (tonic) then jerk (clonic). Tend to be drowsy afterwards.)
  - *Tonic or clonic*

- Focal epilepsy: (Commences with a focal feature which may or may not become generalised)
  - *Simple partial* (Consciousness is not impaired, e.g. focal motor seizure)
  - *Complex partial* (Consciousness is impaired, e.g. olfactory aura)
  - *Secondary generalised tonic clonic*

Seizure type and frequency should be documented as associated risks may vary. Frequency and level of support will be related to this.

Pre-pregnancy management

Women with epilepsy should be informed that they are likely to have a healthy outcome. However, pregnancies in women with epilepsy should be planned if possible as most complications are avoidable.

- Drug therapy

  All anti-epileptic drugs (AEDs) are potentially teratogenic. Prospective data collected by the UK Epilepsy and Pregnancy Register showed only 4.2% of live births to women with epilepsy had an MCM (Major Congenital Malformation). The MCM rate for polytherapy exposure was greater than for monotherapy exposure. Polytherapy regimens containing valproate had significantly more

MCMs than those not containing valproate. For monotherapy exposures, carbamazepine was associated with the lowest risk of MCM.

Aim for lowest possible dose and number of AEDs before and during pregnancy.

Pre-pregnancy withdrawal of AEDs should be considered in those who have been seizure free for at least 2 years. This must only be done under the close supervision of a neurologist. (NOTE: recurrence of seizures will result in a minimum 12 month driving ban and withdrawal of AEDs will result in a minimum 6 month ban).

Epileptics who have not been seizure free for 2 years or those in whom specific epilepsy syndrome requires ongoing treatment should be considered for conversion of multiple drug treatment to monotherapy.

Current evidence suggests that carbamazepine SR carries the lowest risk whilst sodium valporate carries the highest risk.

It is important to remember that risk is associated not only with drug type and dose but also type of seizures and for some of the newer AED's there is no data available.

RISKS OF MAJOR CONJENITAL ABNORMALITIES:

DRUG NAME	DOSAGE	RISK OF CONGENITAL ABNORMALITY (%)
Carbemazepine SR (Tegretol Retard)	<1g/day	2-3%
Lamotrigine (Lamictal)	<200mg/day 400mg/day	2-3% 4-5%
Phenytoin (Epanutin)		5-6%
Sodium Valporate slow release (Epilim Chrono)	<1g/day >1g/day	6% 9%
Gabapentin (Neurontin)		very little data available
Levetiracetam		2.7%

- Epilim also appears to carry a risk of developmental and learning delay of around 15-20%.

With topiramate monotherapy, there is a small increased risk of hypospadias, oral clefts and low birth weight. The increased risk is not regarded as grounds for termination but detailed ultrasound scans to screen the fetus for problems would be recommended. Exposure to topiramate at any stage in pregnancy would not usually be regarded as medical grounds for termination of pregnancy. Features of "Fetal Anticonvulsant Syndrome" include:

Major abnormalities	**Minor abnormalities**
Microcephaly	Hypertelorism
Cleft lip and/or palate	Distal digital and nail hypoplasia
Neural tube defect	Flat nasal bridge
Congenital heart defects	Low set ears
IUGR	Epicanthic folds
Developmental delay	Long philtrum

- Folic acid

AED's are associated with an increased risk of neural tube defect (NTD). Commence folic acid 5mg/day three months prior to conception and continue till the end of first trimester. If the pregnancy is unplanned, commence this dose as soon as the pregnancy is confirmed.

- Contraception
  Consider advising the continuing use of contraception whilst stabilising epileptic control.

- Genetic implications
  If one parent has epilepsy, any offspring has a 4% risk of epilepsy. This increases to 10% if a sibling is affected and 15% if both parents are affected.

Summary of pre-pregnancy advice:

- General health: smoking, alcohol, weight, exercise and rubella immunity
- Maximise seizure control
- Minimise drug therapy
- Folic acid 5mg/day
- Warn re potential teratogenicity and seizure management in pregnancy
- Advise that seizure frequency may alter during pregnancy and medication may need adjusting. Triggers which may exacerbate epilepsy include lack of sleep and missed medication (e.g. secondary to hyperemesis)
- Discuss postnatal childcare issues

Antenatal management

- General management:
  - Pregnant women with epilepsy should be referred for consultant led antenatal care. (At Worcester and Redditch there are dedicated monthly Obstetric Neurology clinics).
  - Offer inclusion on the UK Epilepsy and Pregnancy Register.
  - If not seen pre-pregnancy, review as per pre-pregnancy guidelines.
  - Give general advice regarding coping with morning sickness and avoiding seizure triggers.

- Drug therapy:
  - **Routine monitoring of AEDs in pregnancy is not recommended.** It should be considered if:
    - Increase in seizure frequency
    - Multi-drug therapy
    - Patients on sodium valporate and where toxicity suspected
    - Suspected non compliance
  - Convert poly therapy to mono therapy where possible with guidance from Neurologist.
  - Use lowest therapeutic dose possible and consider use of slow release preparations.
  - Use AED's with lowest teratogenicity risk.
  - If on sodium valporate, avoid high plasma levels by dividing the required daily dose over at least 2 administrations by using a slow release preparation. (If toxicity suspected, check plasma levels).

Scanning during pregnancy:
Routine ultrasound scanning should be performed at 18-20 weeks. Patients on multi drug regimes or with previous baby affected with MCM should have a fetal echocardiogram arranged at 22-24 weeks. Further scans should only be performed if clinically indicated.

- Vitamin K:
  Women on hepatic enzyme inducing AED's like carbamazepine, phenytoin, phenobarbitone, should receive oral Vitamin K 10mg/day from 34 weeks gestation until delivery and 1mg of Vitamin K administered to the baby at birth. (Due to increased risk of haemorrhagic disease of the newborn, secondary to Vitamin K deficiency See Guideline Vitamin K Prophylaxis for Newborn Babies - section for High Risk babies. N.B. babies below 1.5kg receive Vitamin K 0.5mg IM.)

- Emergency treatment: (Status epilepticus)
  Prolonged seizures during pregnancy should be managed as in the non pregnant patient.
  - Position patient to avoid injury. (Ideally in left lateral)
  - Oxygen.
  - Call for help: Anaesthetist and obstetric registrar. (May also need the medical registrar).
  - Seizures are best managed with IV benzodiazepines (lorazepam, diazepam). Diazepam can be used rectally in the absence of IV access. **NOTE: Only one benzodiazepine should be used at a time.**
  - *First choice:* Lorazepam 4mg IV bolus. Maximum rate 2mg/min. May be diluted up to 2ml with 0.9% sodium Chlorider water for injection. Dose may be repeated once after 10 minutes if seizures reoccur. Diazepam 10mg IV bolus. Maximum rate 5mg/min. Can be repeated once after 10 minutes. (Diazepam is also available as a rectal preparation. Rectal tubes 2mg/ml. Dose 10–20 mg, repeated once after 10–15 minutes if necessary
  - If necessary, phenytoin IV at 20mg/kg can be given at a rate no greater than 50mg/minute(maximum 2 gm). This can be concurrent after starting the lorazepam.
  - Advice must be sought from the available neurologist when drugs like Levetiracetam are needed. Levetiracetam is an anticonvulsant available for oral and intravenous use. It has a very good side effect and interaction profile.

    The usual dosage is 500mg BD by IV injection. Alternatively, the drug can be introduced rapidly by mouth to replace the IV formulation, and no drug levels are needed.
  - If still fitting at 30 minutes, then are likely to require intubation.

Management of labour and delivery

- Induction of labour and caesarean section should be performed for obstetric indications only. Vaginal delivery should be the norm. Status epilepticus or recurrent intra-partum seizures may warrant abdominal delivery for fetal indications.
- **Pethidine is contraindicated.** All other forms of analgesia are acceptable.
- Avoid exhaustion (including sleep deprivation) and hyperventilation (especially with the use of Entonox) as this may increase seizure frequency.
- Ensure AEDs are given regularly and doses are NOT omitted during labour.
- There is an increased risk of seizures for the first few days after birth.
- If medication has been increased antenatally, there is an increased risk of toxicity postnatally.
- Seizures in labour should be managed as for "status".

Postnatal care and care of the infant

Convert back to pre pregnancy AED doses if altered during pregnancy.

- Breastfeeding:

- Breastfeeding for most women on AEDs is safe and should be encouraged. However the gestation and health of the neonate should be taken into account.
- All infants should be monitored for sedation, poor feeding, adequate weight gain, and developmental milestones.
- Breastfeeding may help prevent problems in the neonate resulting from sudden withdrawal of the AEDs to which it was exposed *in utero.*
- Sedative AEDs (phenobarbitone, primidone, benzodiazepines) can cause sedation / withdrawal jitters in the infant but are not contraindicated to breastfeeding. If sedation occurs the amount of medication that reaches the baby may be minimised by breastfeeding immediately prior to the dose when the level is lowest. (Refer to the breast feeding coordinator).
- Mothers should be given adequate opportunity to sleep as sleep deprivation may precipitate fits. If possible father or other relative should be encouraged to take responsibility of baby at night: ensure availability of a breast pump to enable use of expressed milk for overnight feeds.
- Advice on drugs in breast milk can be obtained from **Medicines Information on ext. 30235 Monday to Friday 08.30-17.00**

- Safety:

  The introduction of a few safety precautions may help avoid accidents and injury, even if seizures occur.

  - Advise feeding whilst sitting on the floor with back against a wall.
  - Advise epileptic mothers against bedsharing with baby.
  - Bathing of baby should be performed in the presence of others using a sponge down method on a mat on the floor rather than in a bath.
  - Babies should be carried up the stairs in a carrycot.
  - Keep a carrycot / play pen handy, especially if have seizure warnings.
  - House should be made safe and baby proof fires, sockets etc.
  - Provide patient information leaflet prior to discharge home : WAHT leaflet - Looking after a new baby if you have epilepsy/Epilepsy Action leaflet – Mothers in mind http://www.epilepsy.org.uk/downloads/pdf/epilepsyaction_mothersinmind.pdf.

- Contraception:

  There are no contraindications to hormonal / non hormonal methods of contraception for women on **non hepatic enzyme inducing** AEDs.

  AEDs that induce liver enzymes may reduce the contraceptive efficacy of combined contraceptive methods, progestogen-only pills and progestogen-only implants.

  AEDs that induce liver enzymes do not reduce the efficacy of depot medroxyprogesterone acetate (DMPA), the levonorgestrel-releasing intrauterine system or non-hormonal methods

  The progestogen[22]-only pill is not recommended as reliable contraception in women and girls taking enzyme-inducing AEDs

  The progestogen[22] implant is not recommended in women and girls taking enzyme-inducing AEDs

  Combined hormonal contraception (CHC) increases the clearance of lamotrigine and reduces serum lamotrigine levels and may lead to a loss of seizure control. When a woman or girl starts or stops taking these contraceptives, the dose of lamotrigine may need to be adjusted.

  Women on hepatic enzyme inducing drugs (i.e. carbamazepine, phenytoin, phenobarbitone, primidone and topiramate) using the combined oral contraceptive pill should have their dose of

combined oral contraceptive adjusted to provide 50micrograms or more of ethinylestradiol a day and to tricycle (take 3 packets of the pill "back to back" and then have a FOUR day break before restarting the cycle) [unlicensed].. Continue for the duration of treatment with the enzyme-inducing drug and for 4 weeks after stopping. However full contraceptive efficacy cannot be guaranteed therefore other methods are preferable. (Depo-Provera from 6/52 postnatal, and IUCD or Mirena IUS from 4-8/52 post delivery). Refer to NICE Clinical guideline CG137 (http://www..nice.org.uk/Guidance/CG137) and current BNF.

Further advice can be obtained from **Medicines Information on ext. 30235 Monday to Friday 08.30-17.00**