Epilepsy and pregnancy

See also separate articles Epilepsy in Adults, Anticonvulsants used for Generalised Seizures, Anticonvulsants used for Focal Seizures and Status Epilepticus Management.

Appropriate advice should be made available to women with epilepsy; special advice on contraception and pre-conception and also greater levels of care are required in pregnancy, labour and postnatally.

Most pregnant women with epilepsy have a normal pregnancy and childbirth.[1] However, there is an increased risk of teratogenicity associated with the use of anti-epileptic drugs (AEDs), especially if used during the first trimester and also if the patient takes two or more AEDs.

A review of the risks of major congenital malformations and of adverse neurodevelopmental outcomes for antiepileptic drugs by the Commission on Human Medicines in 2020 has confirmed that lamotrigine and levetiracetam are the safer of the medicines reviewed during pregnancy.[2]

Once an unplanned pregnancy is discovered it is usually too late for changes to be made to the epilepsy treatment regimen. The risk of harm to the mother and fetus from convulsive seizures outweighs the risk of continued therapy.[3]

See also separate articles Anticonvulsants used for Generalised Seizures and Anticonvulsants used for Focal Seizures.

NICE summary guidance on valproate use in women of childbearing age[4]

NICE has issued a summary of all guidance related to use of sodium valproate in women with childbearing potential, in light of the well documented teratogenic risks. This includes the following recommendations:

- Valproate should never be used for epilepsy in women with childbearing potential, unless there is no other effective treatment available.
- Treatment must be initiated and supervised by a specialist.
- For women or girls not pregnant or planning pregnancy, the conditions of the pregnancy prevention programme should be met. [5]
- Valproate should if possible be prescribed as monotherapy with a prolonged-release formulation at the lowest effective dose.
- Treatment should be in at least two divided daily doses.
- Women planning to become pregnant should be advised to continue contraception until seen by a specialist, to whom they should be referred urgently.
- Any woman exposed to valproate during pregnancy should be referred with her partner to a specialist in prenatal medicine.
- Women on valproate with unplanned pregnancy should be referred urgently to a specialist, but advised to continue treatment until they are seen.

Contraception

Liver enzyme (cytochrome P-450) induction reduces the efficacy of the combined oral contraceptive pill, combined contraceptive patch, combined contraceptive vaginal ring and progestogen-only contraceptive pill and this may place women at greater risk of unplanned pregnancy.[6] Women should be counselled about the increased risk of pregnancy (contraceptive failure) and any harmful effects of medication on the fetus.

- Women with a history of epilepsy, who are not taking anticonvulsants, may use any method. Women taking anticonvulsants that do not induce liver enzymes (eg, gabapentin, levetiracetam, valproate and vigabatrin) may use any method without restriction.

- Women taking anticonvulsants that induce liver enzymes (eg, phenytoin, carbamazepine, barbiturates, primidone, topiramate and oxcarbazepine) may use depot medroxyprogesterone acetate, copper intrauterine contraceptive devices, the levonorgestrel-releasing intrauterine system, barrier methods and natural family planning methods.
- The progestogen-only contraceptive pill and the progestogen implant are not recommended as reliable contraception in patients taking enzyme-inducing AEDs.
- Intramuscular medroxyprogesterone acetate (Depo-Provera®) can be used but should be scheduled every 10 weeks rather than 12-weekly.
- The use of additional barrier methods should be discussed with women and girls taking enzyme-inducing AEDs and oral contraception or having depot injections of progestogen.[4]
- If women choose a combined contraceptive method, they should use a preparation containing at least 50 micrograms of oestrogen.[6] Tricycling the packs, with no withdrawal bleed for 3-4 packs and then a reduced pill-free interval of only four days, is also recommended.
- Any oestrogen-based contraceptive can result in a significant reduction of lamotrigine levels and lead to loss of seizure control.[4]
- Breakthrough bleeding does not necessarily indicate low serum hormone concentrations and risk of ovulation; nevertheless, women with breakthrough bleeding may increase their dose of ethinylestradiol above 50 micrograms daily.
- After appropriate counselling some women may choose sterilisation as a permanent method of contraception.

Emergency contraception[3]

- The effectiveness of levonorgestrel, and possibly ulipristal, is reduced in women taking enzyme-inducing drugs (and possibly for four weeks after stopping).
- A copper intrauterine contraceptive device can be offered instead, or the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose (unlicensed dose).

- See also the article on Emergency Contraceptives.

Fertility

Women with epilepsy may have a lower fertility rate than average but the evidence is poor. While personal choice and/or societal pressure may play some role in this, women with epilepsy also appear to have a higher incidence of menstrual irregularities, polycystic ovarian disease and reproductive endocrine disorders. All of these may reduce fertility. These are thought to arise both from neuro-endocrine disturbances related to seizure activity as well as the alteration of endogenous sex steroid metabolism in the presence of enzyme-inducing AEDs.[1] There is an increase in polycystic ovaries and hyperandrogenism associated with valproate therapy.[7]

Congenital abnormalities[2]

The risk of congenital malformation is higher in babies if the mother has epilepsy. Most women with epilepsy should continue their medication during pregnancy as uncontrolled seizures also carry a maternal risk.[8]

There is an increased risk of teratogenicity associated with the use of AEDs (especially if used during the first trimester and particularly when taking two or more AEDs). Valproate is associated with the highest risk of major and minor congenital malformations (.[3]

Valproate, in particular, is very teratogenic and evidence supports that use in pregnancy leads to congenital malformations (in particular neural tube defects) and long-term neurodevelopmental effects.[3]

For carbamazepine, phenobarbital, phenytoin, and topiramate, the data showed that use during pregnancy was associated with an increased risk of major congenital malformations. The risk for carbamazepine, phenobarbital, and topiramate was shown to be dose dependent. There is the possibility of adverse effects on neurodevelopment associated with the use of phenobarbital and phenytoin, and an increased risk of intra-uterine growth restriction with phenobarbital, topiramate, and zonisamide.

Female patients should be advised not to stop their antiepileptic treatment without discussing this with their doctor, and to seek urgent medical advice if they are on antiepileptic drugs and think they could be pregnant. Those who are planning a pregnancy should be urgently referred to a specialist for advice on antiepileptic treatment and offered folic acid.

With any antiepileptic drug used during pregnancy, monotherapy and use of the lowest effective dose are recommended where possible.

Fetal valproate syndrome[9]

NB: valproate should not be used during pregnancy or in women of child-bearing age unless there is no safer alternative and only after a careful discussion of the risks.[3]

Children exposed to valproate have more distinctive facial features; however, a subtle and distinctive facial phenotype is also seen in children exposed to carbamazepine. Nearly half of unexposed children had some of the facial features associated with AED exposure, showing that many of these features may be seen as part of normal variation and that the diagnosis of the fetal anticonvulsant syndrome is difficult to make on the basis of facial appearance alone.

Associated features include tall/broad forehead, trigonocephaly (premature fusion of the metopic suture, leading to a triangular-shaped forehead), medial deficiency of eyebrows, infraorbital grooves, epicanthic folds, broad nasal bridge, anteverted nose, abnormal philtrum, thin upper lip, everted lower lip, micrognathia, small mouth, dysplastic ears, hypoplastic digits, arachnodactyly, clinodactyly, flat feet and hypoplastic nails.

One study found that fetal valproate exposure has dose-dependent associations with reduced cognitive abilities at 6 years of age. There was a beneficial association of periconceptional folate with the child's IQ. [10]

Fetal valproate exposure is associated with an increased likelihood of difficulty with adaptive functioning and with attention deficit hyperactivity disorder (ADHD). [11]

Performance IQ has also been found to be significantly lower in children exposed to carbamazepine during pregnancy than in unexposed children. [12]

There are relatively few data regarding the safety of the newer AEDs during pregnancy. However, a study in Denmark found that first-trimester exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin or levetiracetam compared with no exposure was not associated with an increased risk of major birth defects. [13]

Pre-conception [4] [14]

Women who want to become pregnant should be referred to a specialist for advice in advance of conception.

- For some women, the severity of seizure or the seizure type may not pose a serious threat and drug withdrawal may be considered. Treatment may be resumed after the first trimester. If treatment with AEDs must continue throughout pregnancy then monotherapy is preferable at the lowest effective dose.
- The choice of anti-epileptic therapy should also be carefully considered in prepubescent girls who may later become pregnant. [3]
- Discuss the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child. Assess the risks and benefits of treatment with individual drugs.

- It should be emphasised that the likelihood of a woman who is taking AEDs having a baby with no malformations is at least 90%. It is very important that women do not stop taking treatment just because of concern over harm to the fetus and without a thorough specialist assessment of individual need.[3]
- **Folic acid**:[3]
    - To reduce the risk of neural tube defects, folate supplementation is advised before conception and throughout the first trimester.
    - 5 mg per day of folic acid before any possibility of pregnancy should be advised in order to lower the risk of neural tube defects in the offspring.

Antenatal[3] [4] [14]

The concentration of AEDs in the plasma can change during pregnancy. Doses of phenytoin, carbamazepine and lamotrigine should be adjusted on the basis of plasma-drug concentration monitoring. The dose of other AEDs should be monitored carefully during pregnancy and after birth and adjustments made on a clinical basis.

Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to anti-epileptic treatment.

There is an increased risk of complications during pregnancy and labour. Care of pregnant women and girls should be shared between the obstetrician and the epilepsy specialist. All pregnant women and girls with epilepsy should notify their pregnancy to the UK Epilepsy and Pregnancy Register - see website under 'Further reading & references', below.

- An increase in seizure frequency is generally unlikely in pregnancy or in the first few months after birth. The risk of a tonic-clonic seizure during the labour and the 24 hours after birth is low.

- The fetus may be at relatively higher risk of harm during a generalised tonic-clonic (GTC) seizure (although the absolute risk remains low) and the level of risk may depend on seizure frequency. However, miscarriage, trauma related to falls, fetal hypoxia and acidosis are all possible sequelae of maternal seizures. There is no evidence that focal, absence or myoclonic seizures affect the pregnancy or developing fetus adversely unless the mother falls and sustains an injury.
- Status epilepticus carries a high mortality rate for mother and fetus, and generalised seizures occurring during labour can result in fetal bradycardia.
- Other potential antenatal problems seen more frequently in women with epilepsy are hyperemesis gravidarum, gestational hypertension, mild pre-eclampsia, vaginal bleeding and anaemia.[15]
- Difficulties during labour and delivery include premature labour, failure to progress and an increased rate of caesarean sections.[15]

Antenatal and intrapartum care[4]

- Pregnant women taking AEDs should be offered a high-resolution ultrasound scan to screen for structural anomalies, performed at 18-20 weeks of gestation; however, earlier scanning (11-13 weeks) may allow major malformations to be detected sooner.
- Fetal growth should be monitored in women taking topiramate or levetiracetam.[3]
- Genetic counselling should be considered if one partner has epilepsy, particularly if the partner has idiopathic epilepsy and a positive family history of epilepsy.

- Intrapartum care should include the following:[1]
    - Women should deliver in a centre with adequate facilities for maternal and neonatal resuscitation.
    - Women should continue to take their anti-epileptic medication in labour.
    - Birthing pools are not recommended for women with epilepsy.
    - Intravenous access (in case of seizure).
    - Hyperventilation and maternal exhaustion should be avoided.
    - GTC seizures are associated with hypoxia. Continuous cardiotocography (CTG) tracing is recommended in the event of a seizure.
    - An intravenous benzodiazepine (eg, lorazepam or diazepam) is recommended to terminate any seizures.
    - In the event of benzodiazepine being used to terminate the seizure, loss of baseline variability of the fetal heart rate tracing can be expected for approximately one hour.

Postnatal

- Withdrawal effects in the newborn may occur with some AEDs, especially benzodiazepines and phenobarbital.[3]
- If doses have been increased during pregnancy, toxicity may occur and medication requirement is likely to fall in the puerperium.
- Routine injection of vitamin K at birth minimises the risk of neonatal haemorrhage associated with AEDs.[3]

- Breastfeeding:
    - Breastfeeding for most women taking AEDs is generally safe and should be encouraged.[4]
    - All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones.[3]
    - Infants should also be monitored for adverse effects associated with the antiepileptic drug, particularly:[3]
        - With newer antiepileptics.
        - If the antiepileptic is readily transferred into breast-milk causing high infant serum-drug concentrations (eg, ethosuximide, lamotrigine, primidone, and zonisamide).
        - If slower metabolism in the infant causes drugs to accumulate (eg, phenobarbital and lamotrigine).
    - One study found no adverse effects of AED exposure via breast milk observed at age 6 years and found that those children who had been breast-fed exhibited higher IQ and enhanced verbal abilities.[16]
    - The total amount of drug transferred to infants via breast milk is usually much smaller than the amount transferred via the placenta during pregnancy. However, repeated administration of a drug such as lamotrigine via breast milk may lead to accumulation in the infant.[7]
    - Primidone, phenobarbital and the benzodiazepines may cause drowsiness in breast-fed babies.[3]
- Maternity services should be aware of the risk of postpartum seizures, particularly in the setting of sleep deprivation. Ensuring women get adequate sleep and take their medication is very important.
- Mothers may be anxious about the prospect of having a seizure whilst caring for a baby at home alone. Although the risk to the infant from maternal seizures is generally low, women with juvenile myoclonic epilepsy are a particular concern. The myoclonic jerks tend to be more frequent in the early morning, often around the time of infant waking.

- To reduce the risk of injury if the mother has a seizure, advice should include:

    - Change or feed the baby on the floor.
    - Avoid baby slings.
    - Where possible, minimise climbing of stairs.
    - Avoid bathing the baby when alone.

Further reading

- Epilepsy Action
- Epilepsy Society
- Epilepsy Scotland
- Epilepsy Wales
- UK Epilepsy and Pregnancy Register
- Valproate - patient guide; What women and girls need to know about valproate, Nov 2021.
- Epilepsy in Pregnancy - Green-top Guideline No.68; Royal College of Obstetricians and Gynaecologists (2016)

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Authored by:	Peer Reviewed by: Dr Krishna Vakharia, MRCGP	
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