Epilepsy in pregnancy

Dr Naser Al-Husban MD, JBOG, MRCOG, FRCOG

Prevalence

1/200 pregnancies is for an epileptic woman taking anti-epileptic drugs (AED)

- Epilepsy is common, with up to 0.5–1% of the population having active epilepsy, one third of whom are women of childbearing potential

Management Objective

- Avoid convulsive seizures that are harmful for both mother and child while minimising risks from the treatment of epilepsy.

Maternal risks

Mortality

10-fold increase in mortality rate among pregnant women with epilepsy (WWE), which greatly exceeded the two to three-fold mortality rate observed in people with epilepsy. Withdrawal of treatment may have contributed to excess seizure related deaths

Maternal risks

- **Mortality**
- Uncontrolled tonic-clonic seizures are the strongest risk factor for SUDEP, which are the main cause of death in pregnant WWE.
- 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

Maternal risks

Change in seizure frequency

- an increase in seizure frequency in 15–37% of pregnant women, possibly relating to non adherence to medication or sleep deprivation.
- Between 1–2% of women with epilepsy can experience a tonic-clonic seizure in labour and a further 1–2% within the first 24 hours after delivery

Maternal risks

Complications of pregnancy

- Recent studies have not confirmed an increase in complications
- Induction of labour, instrumental deliveries and caesarean sections may be more common in women with epilepsy compared with controls.
- It is unclear if this relates to an increase in medical indications or concern on the part of mothers or their obstetricians

Maternal risks

Effects of pregnancy on AED

- overall reduction in total plasma concentration and the unbound fraction of AEDs during pregnancy, which normalised shortly after delivery.
- Recent evidence suggests that the particularly marked reduction in lamotrigine levels during pregnancy can result in aggravation of seizures in some women
- Measurement of total plasma concentration for most AEDs is unreliable as it does not reflect the free (active) fraction of drug.
- Large interindividual and intra-individual variations of drug levels limit interpretation of routine therapeutic drug monitoring.
- Alterations in dosage should be made on clinical grounds and routine **measurements** are not recommended but can be useful in ascertaining symptoms of **toxicity** or drug **adherence**

Implications for foetal & child development

Seizure

- Tonic-clonic seizures are associated with foetal hypoxia, fetal intracranial haemorrhage and fetal loss.
- The absolute risk from convulsive seizures is unknown and may depend on seizure frequency.
- Non-convulsive seizures are believed to be of little risk to the fetus, but they have psychosocial and socio-economic consequences for the mother.
- The consensus is that the risks of uncontrolled convulsive seizures outweigh the potential teratogenic risk of medication, and women with active epilepsy are advised to continue with medication during pregnancy.

Implications for foetal & child development

Foetal loss

- There is consistent evidence of an approximate two-fold increased risk of spontaneous abortion, stillbirth and perinatal loss among women with epilepsy against the background population rate

Implications for foetal & child development

- **IUGR**
- Most studies reported an association between lower birth weight and AED exposure, ranging up to 200 g.
- The risk of clinically significant low birth weight or small for-gestational age children was highly variable, representing up to a two-fold risk compared with control groups, but few results were statistically significant.
- Much of this higher risk may be associated with the use of polytherapy.

Implications for foetal & child development

Major malformations

- 2–3 fold increase in major malformations
- Most common; congenital heart defects, neural tube defects, urogenital defects (glandular hypospadias) and orofacial clefts
- Absolute rates vary between 1.25–11.5% (2–3% in the general population)
- The risk is highest in the first trimester during organogenesis.
- A teratogenic role for AEDs is suggested by higher rates of malformation among women with treated epilepsy compared with those that are untreated.
- Polytherapy higher risks than monotherapy exposure.
- A dose response effect has been suggested for some AEDs

Implications for foetal & child development

Major malformations

- congenital heart defects and facial clefts are associated with phenytoin, phenobarbital and Primidone
- Valproate has been associated with skeletal defects such as radial aplasia and urogenital defects such as hypospadias.
- Studies suggest a 1% risk of neural tube defect with carbamazepine exposure and a 1–2% risk with valproate exposure.
- a higher risk of malformations with valproate compared with other AEDs in most studies. (valproate 6%, carbamazepine 2.3%, lamotrigine 2.9%)
- Phenytoin; lower risks than other AED

Implications for foetal & child development

Major malformations

- Animal data suggest a teratogenic risk for **topiramate**, but not for **levetiracetam** or **gabapentin.**
- Human data is largely limited to case series and post-marketing surveillance, making firm conclusions difficult.
- The manufacturers recommend their avoidance in pregnancy.
- All studies have consistently shown an increase in major malformations with polytherapy, with a higher risk with increasing numbers of drugs used.
- The reported rates range between 8–25%.
- Higher malformation rates have been reported with particular combinations, especially those including valproate.

Implications for foetal & child development

Minor malformations

- Anomalies are reported to occur in 6–20% of infants exposed to AEDs in utero, representing a two-fold increase over the general population.
- Although a characteristic pattern of minor anomalies has been associated with certain AEDs, there is considerable overlap, and the existence of drug-specific syndromes and their association with more serious problems remains uncertain.
- The combination of characteristic facies with typical major malformations with or without developmental delay is referred to as the fetal anticonvulsant syndrome.

Implications for foetal & child development

Long term developmental effects

- Both retrospective and prospective studies; a higher prevalence of developmental delay, especially in the first two years of life, in children born to mothers with epilepsy compared with controls in the general population
- Results from long-term follow-up to school age have been Conflicting.Few have reported the proportion of children with clinically significant cognitive impairment, with reports varying between 1.7–30%

Implications for foetal & child development

Long term developmental effects

- Several studies have consistently suggested an association with poorer developmental outcomes with valproate exposure.
- A large retrospective study of school age children found a significantly lower mean verbal IQ among those exposed to valproate in utero compared with non-exposed children of mothers with epilepsy and those exposed to carbamazepine or phenytoin.
- Interestingly, five or more tonic-clonic seizures during pregnancy were also independently associated with a lower verbal IQ
- Polytherapy appears to be more commonly associated with poorer developmental outcomes at an early age, but the studies were usually too small to allow firm conclusions

Folic acid

- Evidence from primary and secondary prevention studies have shown that periconceptual folate supplementation lowers the risk of neural tube defect in children of women in the general population
- The optimum dosage of supplementation is not known and ranged between 0.4–4 mg/day
- 5 mg/day of folic acid is recommended before conception and up to at least the end of the first trimester in all women taking AEDs.
- All sexually active women of childbearing age on AEDs should receive folic acid

Haemorrhagic disease of the newborn

- All women on enzyme-inducing AEDs receive oral vitamin K (20 mg/day) from 36 weeks of gestation to delivery.
- A prospective cohort study found no significant risk of neonatal haemorrhage despite lack of oral vitamin K supplementation in mothers taking AEDs, provided that neonates received the standard parenteral injection of 1 mg vitamin K at birth.
- Based on this evidence the National Institute for Health and Clinical Excellence (NICE) guidelines stipulate the need to give only 1 mg of parenteral vitamin K at birth to all children born to mothers taking enzyme-inducing AEDs.

Risks of developing epilepsy

- Human genetic disorders associated with seizures and genetic epilepsies are rare and account for only 1% of cases of epilepsy.
- The risk of unprovoked seizures is higher in offspring of parents with epilepsy onset before 20 years of age than in offspring of those with later onset epilepsy (9% versus 3%).
- Risk is also higher in offspring of parents with a history of absence seizures (9%) than in offspring of those with other generalised (3%) or partial (5%) seizures.

Breastfeeding

Breastfeeding should be encouraged

- The effect of AEDs on infants depends mainly on the AED level in breast milk and the metabolism and elimination half-life of the AED in the neonate
- Phenytoin, carbamazepine and valproate are only found in low concentrations in breast milk as they are all highly protein bound.
- Phenobarbital and primidone reach higher levels as they are less protein bound.
- Lamotrigine and topiramate may be significantly excreted in breast milk, but no adverse effects have been reported

Breastfeeding

- Relatively immature drug metabolism mechanisms and reduced serum protein binding in the infant may lead to drug accumulation. This is particularly true for phenobarbital and primidone.
- Mothers should be advised to look for appropriate weight gain and sleep patterns, and to watch for excessive drowsiness or poor feeding.
- If there is any concern then the AED level in the infant's serum should be measured.

Management and counselling

- potential teratogenic risk of AEDs but also adequate seizure control and wider quality of life issues
- Pre-conceptual counselling should be offered to all women of childbearing age.
- women should be reassured that the majority of pregnancies proceed without difficulties, the risks of major malformations and potential longer term effects should be discussed.
- All women of childbearing potential should receive 5 mg/day of folic acid

Management and counselling

- The same principles apply for withdrawal of AEDs in seizure-free women as in any person with epilepsy.
- This needs to be carefully planned months before conception, and the implications for driving and risks of seizure recurrence need to be discussed

Management and counselling

- Although there is no legislation it is recommended that driving should be suspended from the first reduction in medication up to the first six months after completion of withdrawal.
- For drug changes the advice is more individualised, driving often being suspended for up to three months. Any change in medication or withdrawal should ideally be done pre-conceptually as organogenesis is almost complete in the first trimester.

Management and counselling

- In those women who continue to need treatment the aim should be to achieve seizure control with the lowest possible dose of monotherapy.
- Polytherapy is best avoided where possible
- The choice of AED is determined primarily by the type of epilepsy
- In women with localisation-related epilepsy there are many alternative drugs available, such as carbamazepine.
- For women with idiopathic generalised epilepsy the balance of risks needs careful consideration for each individual.
- There is clinical consensus and observational data indicating the superiority of valproate over other AEDs for seizure control.
- This creates conflict between the desire to control seizures and the desire to avoid adverse effects

Management and counselling

- Although the evidence may not be adequate to justify switching every woman of childbearing age on valproate to an alternative drug, lamotrigine may be a safer alternative for some.

Management and counselling

- Data on the safety in pregnancy of other drugs licensed for idiopathic generalised epilepsy such as topiramate and levetiracetam are inadequate, resulting in the manufacturers advising avoidance of these drugs.
- Abrupt withdrawal or changes in medication are not recommended even in women presenting with an unplanned pregnancy taking high risk medication.
- Changes in medication after the first trimester, when organogenesis is complete, may be considered because of risks to neurodevelopmental delay, but the pros and cons need to be carefully considered.

Management and counselling

- High quality ultrasound scanning to screen for structural anomalies between 18–20 weeks.
- Prenatal screening using serum alphafetoprotein at 15–22 weeks combined with structural ultrasound scan can identify 95% of fetuses with open neural tube defects.
- Fetal echocardiography and imaging of the fetal face may be required.
- Increased surveillance for intrauterine growth retardation.

Management and counselling

- Women with epilepsy should always be delivered in a consultant-led obstetric unit equipped with facilities for maternal and neonatal resuscitation.
- Treatment of seizures during pregnancy and labour should be managed as in any person with epilepsy, and should be in collaboration with an epilepsy team.
- Recurrent or single prolonged tonic-clonic seizures can be terminated with subbuccal midazolam, intravenous lorazepam or rectal diazepam.
- An increase in seizures in the perinatal period can be treated with clobazam 10 mg twice daily if the mother is able to take oral .
- There is limited data on the use of clobazam in pregnancy but benzodiazepines can be associated with sedation in the newborn

Contraception

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

Contraception

- **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.**
- **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**