Management of epilepsy during pregnancy: an update

Introducton

Pregnancy does not cause epilepsy.

But a pregnant woman who has epilepsy (WWE –women with epilepsy) may have seizures more often.

This may be because medicines to treat epilepsy can work differently during pregnancy.

Seizure during pregnancy

Eclampsia is a severe complication of preeclampsia.

It's a rare but serious condition where high blood pressure results in seizures during pregnancy.

This needs to be differentiated from epilepsy in pregnancy.

Seizures are periods of disturbed brain activity that can cause episodes of staring, decreased alertness, and convulsions – and both can occur in pregnancy.

However although most pregnancies and deliveries in WWE are uncomplicated, they and those on AED (anti epileptic drugs) *have an increased risk of preeclampsia* and bleeding in pregnancy. WWE and AED use have an increased risk of preterm birth too.

It’s best to keep a woman with known epilepsy, planning pregnancy under folic acid.

Most experts agree that folic acid supplementation is a *key preconception intervention*, particularly in women with epilepsy who take anti-epileptic drugs (AEDs).

Dosing should be as this - who could possibly become pregnant are advised to consume at least 400 micrograms (mcg)-equivalent to 0.4 milligrams (mg).

For women who have epilepsy, however, some doctors recommend a larger dose, *up to 4 mg daily*.

Primary prevention of neural tube defect through folic acid supplementation results in reduction of risk in an otherwise healthy population by this simple, cheap, easily available drug.

This can prevent foetal anticonvulsant syndrome (FAS) during pregnancy.

FAS is a group of malformations that can affect some babies if they are exposed to certain medicines, (AEDs), while in the womb. Malformations include spina bifida, cleft palate, heart defects, learning problems and autism spectrum disorder.

A very common question faced gynaecologists is - Is it safe to have a baby when you have epilepsy?

The answer is - there is a higher risk of having a child with epilepsy if one or both parents has epilepsy, generalized epilepsy or if the parents' seizures started early in life.

While epilepsy can affect pregnancy, with proper medical care, *more than 90% of women with epilepsy can expect a safe pregnancy and a healthy baby* even in (WWE).

However pregnancy can lower seizure threshold due to multiple factors.

Pregnancy is associated with a number of physiological, endocrine and psychological changes, *any or all of which might contribute to lowering the seizure threshold*.

Physiological changes during pregnancy alter the pharmacokinetics of AEDs, which may result in lower levels and seizure deterioration in WWE.

Treatment

The clinical management of women with epilepsy on antiepileptic drugs (AEDs) during pregnancy presents unique challenges.

The goal of treatment is optimal seizure control with minimal *in utero* foetal exposure to AEDs in an effort to reduce the risk of structural and neurodevelopmental teratogenic effects.

The clinical management of women with epilepsy on (AEDs) during pregnancy presents unique challenges.

Women with epilepsy (WWE) are advised to continue antiepileptic drugs (AEDs) during pregnancy to reduce maternal and foetal trauma associated with seizures.

There is no need to change so called safe drugs in pregnancy if a patient with epilepsy id already well controlled. The goal is optimal seizure control with minimum foetal exposure to AEDs.

Prenatal exposure to AEDs may be associated with major congenital malformations (MCM), intrauterine growth retardation, dysmorphic syndromes and deficits in neurocognitive development. These issues cause great concern in WWE who are thinking about having children.

In the past, counselling WWE was challenging because little information was available about specific drugs and other commonly encountered situations.

Seizure deterioration may be attributed to multiple factors, including but not limited to noncompliance, reduction in plasma AED concentration and changes in AED metabolism, and possibly hormonal changes, sleep deprivation and psychosocial stress, although the latter factors have not been studied systematically.

Antiepileptic drug levels during pregnancy

During pregnancy, plasma AED concentrations may fluctuate due to physiologic changes in absorption, increases in renal clearance, altered hepatic clearance, increases in plasma volume distribution and hepatic enzymatic induction from female sex steroid hormones

In pregnancy, drug absorption may be altered due to decreased gastric tone and motility.

Nausea and vomiting may affect drug ingestion, especially during the first trimester.

Volume of distribution increases with weight gain and increases in plasma volume. An increase in total body water, results in a 40–50% increase in plasma volume during pregnancy.

In general, increased clearance may affect AED concentrations and require dose adjustment to maintain pre pregnancy levels. A reduction in AED blood levels >35% from baseline pre pregnancy levels may result in increased seizures for some patients.

Ideally, target AED plasma concentrations should be determined for individual patients based on seizure history and therapeutic concentrations during preconception planning. It is a goal to maintain this target AED level throughout pregnancy in an effort to avoid seizures.

Comparison of different AEDs

The AEDs that have the lowest rates of MCM, such as LTG(Lamotrigine), levetiracetam (LEV) and oxcarbazepine (OXC), are often preferred for WWE who are contemplating pregnancy. These AEDs have increased clearance with changes in plasma drug levels during pregnancy and require close monitoring. *Several studies have documented an increase in clearance of LTG and LEV during pregnancy.*

LTG clearance had marked variability with repeat singleton pregnancies, suggesting that the changes in LTG clearance observed in the first pregnancy may not be replicated in the second pregnancy for the same patient.

The majority of the women (77%) displayed a marked increase in LTG clearance whereas 23% had a minimal increase in LTG clearance from baseline.

LEV also has increased clearance during pregnancy. In one study, LEV concentrations during the third trimester were 60% lower than baseline concentrations outside pregnancy. Clearance of LEV was significantly higher during the third trimester.

With regard to OXC, there is an increase in elimination of the OXC active metabolite 10-monohydroxy-10, 11-dihydro-carbamazepine (MHD) compared with pre pregnancy levels.

In a retrospective study of 13 patients on OXC monotherapy found an increase in elimination of MHD compared with pre pregnancy levels. This decrease in MHD was associated with seizure deterioration in nearly 64% of the patients.

The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) study group reported that 58.5% of patient on OXC monotherapy had seizures during pregnancy or

delivery. Additionally, in the EURAP study the use of OXC monotherapy was associated with a greater risk of convulsive seizures compared to other AED treatment regiments.

Despite multiple factors that favour use of the second or third generation AEDs, many patients worldwide only have access to older AEDs.

The pharmacokinetics of the older AEDs, such as CBZ, phenobarbital (PB), phenytoin (PHT) and VPA, during pregnancy have been reviewed in a few studies. Studies have documented a reduction in total plasma concentration of older AEDs during pregnancy, with a peak decrease in the third trimester.

Aside from CBZ, other commonly used AEDs worldwide are PHT, VPA and PB. These AEDs are not ideal during pregnancy, but they are often the only available AEDs in many developing countries.

Total PB concentration decreased by 55% in pregnancy, with the sharpest decrease noted in the first trimester, and unbound PB concentration decreases by 50%.

Total PHT concentration decreased by 56–61%, with the sharpest decrease in the first trimester and the unbound concentration decreased by 18–33% in pregnancy.

VPA concentrations were found to decrease by 39% throughout the pregnancy and unbound VPA levels to decrease by 22%.

Antenatal vitamin K is administered widely for women taking hepatic enzyme-inducing AED (EIAED) to avoid bleeding in the newborn. However, studies have not supported this practice.

Studies highlight that therapeutic drug monitoring is effective with some AEDs in preventing seizure deterioration for WWE during pregnancy. Additionally, the AEDs that are frequently used during pregnancy, LTG and LEV, have a high clearance and concentrations should be monitored closely during pregnancy to prevent a decrease by more than 35% from preconception baseline and seizure deterioration.

For the AEDs with high protein binding, clearance of total plasma AED and unbound fractions vary. Therapeutic drug monitoring is important during pregnancy in WWE.

Therapeutic drug monitoring of AED levels throughout pregnancy and maintaining target pre pregnancy AED levels may help prevent seizure deterioration during pregnancy.

Major congenital malformations: evidence from pregnancy registries

Foetal structural teratogenicity associated with *in utero* AED exposures has been investigated in several worldwide pregnancy registries, which are prospective observational studies.

MCM are generally defined as 'structural abnormalities of surgical, medical, functional, or cosmetic importance' which occur during organogenesis in the first trimester.

Data from pregnancy registries have consistently shown, in monotherapy and polytherapy, that VPA is associated with the highest rates of fetal MCM, followed by PB and topiramate (TPM).

Higher doses of VPA result in even higher MCM rates.

In utero exposure to polytherapy AED has been associated with higher rates of fetal MCM compared with monotherapy AED in general, but more recent publications highlight that this is an oversimplification.

Obstetrical risk during delivery in WWE

Women with epilepsy may be at increased risk for obstetrical complications. A large, retrospective cohort study of WWE and women without epilepsy (WWoE) found WWE are at higher obstetrical risk.

Women with epilepsy had more than a 10-fold increased risk of death , caesarean section, preeclampsia, seizures during preeclampsia, induced labour, severe postpartum haemorrhage, premature delivery, experience of premature rupture of membranes, developed chorioamnionitis and had longer hospital stay (more than 6 days) compared with WWoE .

WWE, especially those on AEDs, should be educated on possible obstetrical complications during delivery. Due to higher obstetrical complications, WWE should be monitored carefully during delivery.

Additionally, WWE should be encouraged to follow with a doctor trained in obstetrics and gynecology whom may manage potential obstetrical complications during delivery in conjunction with neurologists.

Breast feeding and AEDs

Breast feeding newborns provide numerous benefits to maternal and infant well-being. However, many women have concerns about prolonging their baby's exposure to AEDs beyond gestation *via* breast milk. The benefits of breastfeeding *versus* the theoretical risk of drug exposure in the neonate should be discussed with the patient as well as her delivery team and pediatrician.

Infant exposure to AEDs in breast milk varies depending on multiple factors such as maternal plasma drug concentration, the milk/plasma ratio of the drug, the milk volume ingested by infant, and the absorption, metabolism and excretion of the drug in the infant.

Even though an AED may appear in the breast milk, the degree of medication exposure to the newborn is still likely to be less than the degree of exposure during gestation.

In general, AEDs with minimal protein binding and greater lipid solubility tend to distribute more readily into breast milk.

Some AEDs such as PRM, LVT, GBP, LTG and TPM penetrate into breast milk in relatively high enough concentrations with the potential for clinical effects on the newborn.

Other AEDs that are highly protein bound, such as VPA, PB, PHT and CBZ, do not to penetrate into breast milk in substantially high concentrations

Case series have not reported adverse effects on the newborn of AED exposure *via* breast milk, with the exception of some reports of sedation with the barbiturates and benzodiazepines.

To minimize infant AED exposure, maternal AEDs should be kept to a low effective dose, and if signs of potential adverse reactions are noted (lethargy, poor feeding), infant serum concentrations can be monitored though is it not done routinely.

The benefits of breastfeeding outweigh the risks to the infant. WWE taking AEDs should be encouraged to breast feed their baby if they choose, although many will supplement with 1–2 bottles per 24 hours to allow 1 period of more sustained sleep.

The NEAD study investigated the effects of breastfeeding on child cognitive development.

They found there was no significant difference in the IQs of children tested at age 3 years old of children who were breast fed by mothers taking AEDs (CBZ, LTG, PHT or VPA monotherapy) compared with children who were not breastfed.

A follow-up 6-year study found similar results, but also found that breastfed children had a higher IQ (by 4 points) and increased verbal abilities (by 4 points) even after adjusting for confounding variables such as maternal IQ, AED dose and *periconception folate use*.

Children who were continuously breastfed had favourable outcomes, despite maternal use of AEDs.

Interesting, they found that continuous breastfeeding was less common for women taking AEDs. This highlights that some WWE on AEDs may feel reluctant to breastfeed their infants to prevent AED exposure via *breast milk. It is important for providers to encourage and raise awareness that the benefits of breastfeeding outweigh the risk to the infant.*

First time seizures during pregnancy

- Are relatively rare.
- Episodes concerning for seizure during pregnancy may mimic seizures or may be epileptic seizures.
- First epileptic seizures during pregnancy may be initial presentations of epilepsy.
- In women with epilepsy, seizure frequency and severity can be affected during pregnancy by factors such as changes in ASD (anti-seizure drug) metabolism, changes in hormone levels, and medication compliance.
- Some women with epilepsy experience seizure worsening during pregnancy, while others have an improvement.
- Most epileptic seizures during pregnancy occur in women with pre-existing epilepsy.

- Rarely, women develop new-onset seizure-like episodes concerning for epileptic seizures during pregnancy, posing a diagnostic and therapeutic challenge for the physician.
- New onset seizures during pregnancy were rare. Most women with first-time epileptic seizures during pregnancy also had epileptic seizures after pregnancy, indicating a first presentation of epilepsy.

Summary

- *Pregnancy does not cause epilepsy*. But a pregnant woman who has epilepsy may have seizures more often. This may be because medicines to treat epilepsy can work differently during pregnancy.

- A review of the risks of major congenital malformations and of adverse neurodevelopmental outcomes for antiepileptic drugs by the Commission on Human Medicines has confirmed that *lamotrigine (Lamictal) and levetiracetam* are the safer of the medicines reviewed during pregnancy.

- The AAN (American academy of Neurology) practice parameters concluded that valproate monotherapy possessed increased risk of MCMs compared to phenobarbitol, carbamazepine, phenytoin and lamotrigine The AAN recommended avoidance of valproate in the first trimester of pregnancy due to this risk

- *Most women on anti-seizure medication can have a safe and successful pregnancy*. Some anti-seizure medications are safer than others in pregnancy.

- Similar to valproic acid, carbamazepine increases the risk of neural tube defects; however, **it does not increase the risk of other malformations**. Carbamazepine is also not associated with an increased risk of developmental delay.

- Recent studies carried out by the Commission on Human Medicines (CHM), looking at the risks associated with commonly prescribed AEDs shows that lamotrigine (Lamictal) and levetiracetam (Keppra) **are safer to use during pregnancy than** other AEDs, having low rates of physical birth abnormalities.

- Hence it's useful to start Folate in couples planning pregnancy. It's advisable to be in contact with a neurologist in WWE. 1st seizure is an important issue during pregnancy and should be cautiously dealt. AED taking controlled WWE need not change drug during pregnancy. Breast feeding has no harm. Eclampsia should not be confused with epilepsy.

- Pregnancy makes a female complete as a boon of Motherhood and Epilepsy is in no way to deprive a lady from enjoying safe motherhood.