EPILEPSY IN PREGNANCY: A REVIEW
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Abstract: Epilepsy is one of the common chronic disorders affecting women of reproductive age. The management of epilepsy in pregnancy involves a balance between adequate seizure control vis-à-vis minimizing exposure to antiepileptic drugs to avoid adverse effects to the foetus in-utero. This review addresses critical issues pertaining to women with epilepsy in pregnancy like occurrence of seizures, congenital malformations, perinatal and neonatal outcomes and childhood morbidity.

Keywords: Epilepsy; Pregnancy; Teratogenicity; Seizure; Antiepileptic drugs

Introduction
Epilepsy is one of the common medical disorders affecting women of reproductive age group. The prevalence of epilepsy in pregnancy is 0.5-1%. Pregnancy is associated with a lowered seizure threshold, the cause of which is multifactorial. Women with epilepsy are also at increased risk for a range of perinatal complications including preeclampsia, preterm labour, and foetal morbidity. The goal of obstetric management of women with epilepsy (WWE) is appropriate preconceptional counselling and optimal seizure control during pregnancy with minimal in-utero exposure to antiepileptic drugs (AEDs). This review aims to address certain critical issues pertaining to these women like risk of foetal malformations, obstetric complications, perinatal and neonatal complications and childhood and long-term outcomes of offspring.

A literature review was completed to identify recent studies pertaining to WWE and pregnancy. The PubMed database was searched with several key phrases including ‘management and treatment of women with epilepsy and pregnancy’, ‘AEDs management during pregnancy’, ‘side effects of AEDs during pregnancy’, ‘congenital malformations with embryonic and foetal exposure to AEDs’, ‘neurodevelopment of foetuses exposed to AEDs in-utero’, ‘obstetrical risk, perinatal outcomes of WWE’. In addition, we searched bibliographies of review articles, original articles, established guidelines and book chapters on this topic.

Preconceptional counselling
Preconceptional counselling is a vital part of holistic management of WWE and should include information regarding risks associated with epilepsy and pregnancy, potential interactions with oral contraceptive therapy, and recommended folate supplementation. Low serum folate levels in women with epilepsy are independently associated with an increased risk of major foetal malformations. The Medical Research Council (MRC) vitamin study (which excluded women with epilepsy) demonstrated that folic acid supplementation (4 mg per day) starting before pregnancy was associated with a 72% reduction in the incidence of neural tube defects in women at high risk because of a previously affected pregnancy. Published clinical guidelines regarding the dose of folate supplementation in women with epilepsy vary and are not definitive. The 2009 American Academy of Neurology and American Epilepsy Society guidelines state that data are insufficient to determine whether doses higher than 0.4 mg offer greater protective benefits. In contrast, the American College of Obstetricians and Gynaecologists recommend 4.0 mg of folic acid daily for women at risk of having offspring with neural tube defects (including women taking antiseizure drugs). The higher dose of folic acid has not been associated with adverse effects.

The goal of pre-conceptional counselling is to optimize AEDs therapy and ensure optimum seizure-free interval prior to conception. Regarding AEDs, most of the reviewed studies reinforce that valproic acid (VPA) use should be avoided in women of childbearing age whenever possible. VPA used in combination with other AEDs should be switched over to monotherapy with safer alternatives. Lamotrigine (LTG) and levetiracetam (LEV) are comparatively less teratogenic and are therefore the favourable agents for women who are planning to conceive. According to the North American AED Pregnancy Registry (NAAPR) of the United States, women unexposed to AEDs had a 1.1% risk of major congenital malformations (MCM) which is comparable to that of the general population (2-3%). Among those taking AEDs, risk was highest for VPA at 9.3% (95% confidence interval [CI] 6.4–13.0), followed by Phenobarbital (PB) at 5.5% (95% CI: 2.8–9.7), Topiramate (TP) at 4.2% (95% CI: 2.4–6.8), Carbamazepine (CBZ) at 3.0% (95% CI: 2.1–4.2) and Phenytoin (PHT) at 2.9% (95% CI: 1.5–5.0).

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Lowermost risk was seen with Lamotrigine (LTG) at 2.0% (95% CI: 1.4–2.8) and Levetiracetam (LCT) at 2.4% (95% CI: 1.2–4.3).\(^1\) Cardiac defects were the most commonly reported malformation; PB >150 mg per day had the highest percentage (8%) followed by VPA (7%). Parental history of MCM was associated with a four-fold greater risk in foetal MCM. Lastly, seizure episodes were not associated with a higher risk for MCM.\(^8\)

Women should be counselled that majority (67%) will not experience a seizure in pregnancy. The seizure-free duration is the most crucial factor in assessing the risk of seizure deterioration. In one study, of women who were seizure free for at least 9 months to 1 year prior to pregnancy, 74–92% continued to be seizure free in pregnancy.\(^7\) A study by Abe et al evaluated whether planning of pregnancy in WWE affects seizure control and impacts maternal and neonatal outcomes. In their retrospective cohort study of 153 WWE, compared to the unplanned-pregnancy group, the planned-pregnancy group showed a significantly greater proportion of patients receiving monotherapy with antiepileptic drugs (80% vs. 61%; planned vs. unplanned, \(p = 0.049\)) and those not requiring valproic acid (77% vs. 56%, \(p = 0.031\)). Furthermore, the frequency of epileptic seizures (16% vs. 35%, \(p = 0.018\)) and changes in antiepileptic drugs (24% vs. 41%, \(p = 0.042\)) were significantly lower in the planned-pregnancy group than in the unplanned-pregnancy group.\(^8\) However, no significant intergroup differences were noted in the obstetric complications and neonatal outcomes, including congenital malformations.

The various drugs and associated malformations have been summarised in (Table 1).

### Table 1. Various drugs and associated malformations

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RISK</th>
<th>MALFORMATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>9%</td>
<td>Neural tube defects, cardiovascular, urogenital malformations, minor craniofacial, skeletal, and genital anomalies</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>2.9%</td>
<td>Orofacial clefts, cardiac malformations, genital defects, neuroblastoma</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>5.5%</td>
<td>Cardiac, oro facial, urogenital malformations</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3%</td>
<td>Spina bifida aperta, urogenital malformations</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.9-3.2%</td>
<td>Facial clefts, mostly data reassuring</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0.7%</td>
<td>Low risk</td>
</tr>
<tr>
<td>Topiramate</td>
<td>1.4%</td>
<td>Facial clefts, Small for gestational age (SGA)</td>
</tr>
</tbody>
</table>

\(\text{Data from NAAPR}^6, \text{Hernandez et al (2012)}\)

### Obstetric complications in WWE

Most of the available data has focused on seizure frequency in pregnancy and risk of congenital malformations in women exposed to AEDs. There are very few good quality studies on obstetric outcomes in WWE, however the available evidence suggests that these women are at a higher risk of obstetric complications.

The largest retrospective cohort study comparing 69,385 WWE and 20,449,532 women without epilepsy by MacDonald et al found a 10-fold increased risk of death [adjusted odds ratio (OR) 11.46, 95% CI: 8.64–15.19], caesarean section (adjusted OR 1.40, 95% CI: 1.38–1.42) and labour induction (adjusted OR 1.14, 95% CI: 1.12–1.16) in these women. The risk of pregnancy complications like preeclampsia (adjusted OR 1.59, 95% CI: 1.54–1.63), preterm labour (adjusted OR 1.54, 95% CI: 1.50–1.57) and preterm premature rupture of membranes (adjusted OR 1.07, 95% CI: 1.03–1.11) were also significantly increased.\(^9\)

A population-based cohort study in Norway compared obstetric complications in WWE who were on AEDs with those not on treatment and found WWE on AED were at an increased risk of mild preeclampsia (OR 1.8, 95% CI: 1.3–2.4), gestational hypertension (OR 1.5, 95% CI: 1.0–2.2), antepartum haemorrhage (OR 1.9, 95% CI: 1.1–3.2) and preterm delivery (OR 1.5, 95% CI: 1.1–2.0).\(^10\)

A large meta-analysis of smaller studies by Viale et al concluded that WWE versus those without (2,809,984 pregnancies) had increased odds of spontaneous miscarriage (OR 1·54, 95% CI: 1·02–2·32; \(I^2 = 67\%\)), antepartum haemorrhage (1·49, 1·01–2·00; \(I^2 = 37\%\)), post-partum haemorrhage (1·29, 1·13–1·49; \(I^2 = 41\%\)), hypertensive disorders (1·37, 1·21–1·55; \(I^2 = 23\%\)), induction of labour (1·67, 1·31–2·11; \(I^2 = 64\%\)), caesarean section (1·40, 1·23–1·58; \(I^2 = 66\%\)) and any preterm birth (1·16, 1·01–1·34; \(I^2 = 64\%\)).\(^11\)

### Labour and delivery

Most women have a normal vaginal delivery. However, elective caesarean section may be justified in women with frequent seizures during the third trimester or a history of status epilepticus during severe stress. Generalized tonicclonic seizures (GTCS) may occur during labour in 1-2% of women with epilepsy, and in another 1-2% within 24 hours after delivery.\(^12\) It is therefore essential to maintain a plasma AEDs level known to protect against seizures during the third trimester and during delivery. Doses must not be missed during the period of labour and some women may require additional bolus doses of AEDs to tide over the period of stress. Convulsive seizures during labour and delivery should be treated promptly with intravenous benzodiazepines; lorazepam is considered the drug of choice. Intravenous...
Phenytoin is also highly effective and has a longer duration of action. Generalized tonic clonic seizures can be associated with hypoxia; continuous foetal heart rate monitoring is recommended in the event of a seizure, as well as for a period of at least an hour after administration of benzodiazepines.11

**Breastfeeding and contraception**

All the antiseizure drugs are measurable in breast milk, the reported percentage of maternal plasma levels in breast milk varies from 5-10% with VPA to 90% with ethosuximide.14 However, most experts believe that taking antiseizure drugs does not generally contraindicate breast feeding, as probably benefits outweigh risks and WWE should be counselled regarding the same.

Women should also be aware that efficacy of hormonal contraception may be reduced when taken with AEDs, especially drugs which are inducers of hepatic cytochrome P-450 system. Hence, long-acting reversible contraceptive methods like intra-uterine devices and injectable preparations are preferred methods of contraception in these women. Post-placental insertion of intra-uterine device seems to be a cost-effective and efficacious method in India.

**Perinatal outcomes in WWE**

Neonates born to WWE are at higher risk for perinatal complications such as low birth weight, small for gestational age (SGA), respiratory morbidity and admission to a neonatal care unit (NICU). In a large prospective observational study by Pennell et al, a secondary analysis revealed that SGA was highest for neonates exposed to VPA (14.5%) and CBZ (12.9%). The PHT and VPA groups were noted to have low (<7) 1-minute Apgar scores.15 Data from the European Registry of Antiepileptic Drugs and Pregnancy (EURAP) registry, which followed 129 singleton pregnancies, found that AEDs polytherapy was associated with higher risk of SGA as compared to monotherapy. They also found that occurrence of seizures during pregnancy was associated with shorter gestational age, prematurity and lower birth weight in primiparous women.16 In the meta-analysis by Viale et al, they found increased risk of delivering SGA baby in WWE (OR 1:26 95% CI: 1:20–1:33; p<0.00001), however other infant outcomes such as foetal death, perinatal death, and admission to the NICU were not increased.17

Another observed risk is the incidence of haemorrhagic phenomena in neonates born to mothers on AEDs. This is commonly seen in women taking enzyme-inducing drugs like phenobarbital, hydantoin, carbamazepine, valproic acid, ethosuximide and vigabatrin. Studies have evaluated the role of prophylactic vitamin K administration to such women in the last trimester of pregnancy. One larger study prospectively followed 662 pregnancies in WWE. None of the mothers received vitamin K and they found no difference in the two groups. Bleeding was observed in 0.7% of the offsprings exposed to maternal enzyme-inducing drugs versus 0.4% in the control group which was insignificant.17 The Royal College of Obstetrics and Gynaecology practice guidelines for WWE state that there is insufficient evidence to recommend routine maternal use of oral vitamin K to prevent haemorrhagic disease of the newborn in WWE taking enzyme-inducing AEDs. However, all babies born to WWE taking enzyme-inducing AEDs should be offered 1 mg of intramuscular vitamin K to prevent haemorrhagic disease of the newborn.18

**Infant AED exposure and long-term neurocognitive outcomes**

Exposure to AEDs in utero has been reportedly associated with higher risk of neurocognitive impairment. This was first addressed in the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study by Meador et al who enrolled WWE on a single antiepileptic agent. They found that children exposed to valproate in-utero had significantly lower IQ scores than those exposed to other AEDs. Children exposed to VPA had an IQ score 9 points lower than the score of those exposed to other drugs.19 Significant independent predictors of a child’s IQ were AED type and dose, older gestational age, use of periconceptional folate and higher maternal IQ. Children of mothers taking periconceptional folic acid had a higher mean IQ (108) compared with 101 in the children of mothers who were not taking periconceptional folate. Another population-based study by Christensen et al., found a significantly increased risk of autism spectrum disorder (absolute risk (AR) 4.42%; 95% CI: 2.59%-7.46%) and childhood autism (AR 2.50%; 95% CI: 1.30%-4.81%).20 These findings are similar to those of Wood et al who used the Childhood Autism Rating Scale (CARS) to determine risk of autism in 103 children with in-utero exposure to AED; they determined higher doses of VPA use were associated with autistic traits, especially those in the group exposed to VPA polytherapy (47%).21

**Conclusion**

The clinical management of WWE on AEDs during pregnancy is challenging. The goal of treatment is optimal seizure control with minimal in-utero foetal exposure to AEDs to reduce the risk of structural and neurodevelopmental teratogenic effects. Patients should be carefully educated on potential major congenital malformation, neurodevelopmental outcomes, obstetrical risks, perinatal complications and breast feeding while on AEDs. It is important to monitor WWE during pregnancy, and they should preferably be managed in a tertiary centre concurrent with neurologist expertise. It is also important to highlight that majority of WWE have healthy pregnancies.
References


