CORRESPONDENCE

Need for ‘teratovigilance’ in women with epilepsy on anti-epileptic drugs

‘Off label’ use of many newer anti-epileptic drugs (AEDs) has been approved for treatment of epilepsy with a parallel increase in their use for non-epileptic conditions over the last decade.¹ The information on their safety profile in pregnancy through clinical trials is often not available due to pregnancy being as exclusion criteria. While, a number of older AEDs are reported to cause adverse pregnancy and neonatal outcomes, data regarding newer AEDs is lacking.

The present cross sectional, prospective/retrospective, observational study examined influence of AEDs on pregnancy and neonatal outcomes following approval of Institutional Ethics Review Board. Women with epilepsy (WWE) and pregnancy reporting at Neurology outpatient clinic receiving AEDs, who consented to participate, were enrolled. Data on neurological assessment and pregnancy were collected in a case record form (CRF) modified from International European Registry of Anti-epileptic Drugs and Pregnancy (EURAP).

Data on demography, pregnancy, AED treatment and investigations was recorded. Fetal/neonatal status assessed during antenatal, perinatal and postnatal periods at each clinic visit was entered. The pregnancy and neonatal outcomes were evaluated through pregnancy charts, birth reports and medical records including discharge notes by obstetrician and neonatologist/pediatrician when available. Data was analyzed descriptively and tabulated as frequencies and percentages.

A total of 114/143 (79.7%) pregnant WWE completed the study with 29 dropouts. The age range was 17-35 yrs (25.00 ± 4.00). The data was collected retrospectively at the time of delivery for 26/114 (22.8%) WWE.

The seizure types were generalized tonic clonic seizure (GTCS) in 17 (14.9%), focal in 88 (77.2%) and 9 (7.9%) were unknown. Majority received carbamazepine (CBZ) monotherapy 91 (79.8%) followed by phenobarbitone (PB) and phenytoin (PHT); while 18 (15.8%) received dual and 5(4.4%) received triple therapy (> 2 AEDs). Among newer AEDs 20 received monotherapy and 3 polytherapy (20.2%) either with levetiracetam (LEV), topiramate (TPM), lamotrigine (LTG), or oxcarbamazepine (OxCBZ). The AED treatment pattern remained unchanged during pregnancy in 100 (87.7%) WWE. All received folic acid (FA) 5 mg/day, from the time of confirmation of pregnancy. Seizure control was complete in 85/114 (74.6%) and remaining 29 (25.4%) had seizures during first, second and/or third trimester.

There were 111 live births, one twin delivery. The mode of delivery was vaginal in 65/111 (58.6%), forceps in 3/111 (2.70%) and lower segment caesarean section in 43 (38.7%). Adverse pregnancy outcomes were seen in six WWE who received older AEDs of which 5 had received monotherapy and one dual therapy. There were 2 abortions and 3 perinatal deaths. The neonatal adverse outcomes included low birth weight in 33 (28.9%), critically low Apgar score of 3/10 in one, seizures in 2 and 7 (7.14%) had malformations in WWE who had received CBZ and PHT (Table 1).

Majority of WWE had partial seizures with no increase in their frequency or worsening during pregnancy indicating good treatment practice, a finding similar to Marcele et al.² While, this observation may support optimal seizure control it does not assist in concluding appropriateness of AED or their compliance.

Country specific registries have been initiated to monitor pregnancy and neonatal outcomes in WWE receiving AEDs to report congenital malformations (CM). Such approach is proposed to assist in making suitable recommendations for use of AEDs, to minimize occurrence of CMs (EURAP).³
The observed malformations 7/112 (6.1%) new born was higher than in Europe (6.0%) and UK (4.2%). The potential teratogenic effect observed with CBZ could be due to metabolite CBZ-Epoxide, or oxidation of CBZ-Epoxide or CBZ at positions on aromatic ring leading to formation of reactive intermediates - arene oxides or quinones in mouse model. However, involvement of such mechanisms in inducing fetal teratogenic effects in humans is not clear. The conventional AED phenytoin (PHT) is reported to induce teratogenicity due to its interference with folate metabolism.

Extent of use of newer AEDs in present study was minimal (12.3%), and was similar to that reported by Kochen et al. from Argentina and Latin America. Study by Katriina et al. in Kuopio University Hospital, Finland reported higher rates of prenatal and neonatal complications. The various prenatal complications in our study were similar and included - abortions, perinatal deaths, forceps, cesarean delivery, and adverse neonatal outcomes such as low Apgar score, neonatal seizures and low birth weight. The neonatal complications in our study were primarily seen with enzyme inducing AED monotherapy such as CBZ and PHT, while study by Montouris et al. have shown frequent neonatal malformations in WWE who received AED polytherapy. The overall occurrence of CMs in our study was 6.1% of which 5/7 had received AED monotherapy including a single case treated with LTG and low dose clonazepam associated with multiple anomalies - hydrocephalus, ascites, polydactyly and in utero fetal death.

A few limitations to our study include – patient’s irregular visits, high dropout rate, and incomplete information due to retrospective data collection and hence inability to identify risk factors responsible for observed malformations. However, findings of study add supportive evidence indicating enzyme-inducing AEDs like CBZ and PHT, are responsible for observed malformations. The use of newer AEDs appears to be in favor of women of child bearing age and anticipated to reduce observed adverse pregnancy and neonatal outcomes.

In conclusion we suggest need for teratovigilance studies to establish criteria for selection of safer AED options in improving pregnancy and neonatal outcomes as pregnant WWE represent a challenging population in neurological practice.

### Table 1: Neonatal outcomes in women with epilepsy (WWE) to show distribution of congenital malformations (n=7)

<table>
<thead>
<tr>
<th>Congenital malformations</th>
<th>No. of WWE</th>
<th>Pattern of AED use</th>
<th>Total daily AED dose range in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydronephrosis secondary to ureteropelvic junction obstruction</td>
<td>1</td>
<td>Carbamazepine</td>
<td>400 - 600</td>
</tr>
<tr>
<td>Mild pelvicaliectasis and ureteropelvic junction obstruction</td>
<td>1</td>
<td>Carbamazepine</td>
<td>400 - 600</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>1</td>
<td>Phenytoin</td>
<td>200 - 300</td>
</tr>
<tr>
<td>Hip dysplasia</td>
<td>1</td>
<td>Phenytoin</td>
<td>200</td>
</tr>
<tr>
<td>Club feet</td>
<td>1</td>
<td>Lamotrigine</td>
<td>1000</td>
</tr>
<tr>
<td>Intrauterine death (IUD) with multiple anomalies</td>
<td>1</td>
<td>Lamotrigine + clonazepam</td>
<td>100-300 + 0.25-0.5</td>
</tr>
<tr>
<td>Hypo plastic ear, facial palsy</td>
<td>1</td>
<td>Phenytoin + carbamazepine</td>
<td>100 + 400</td>
</tr>
</tbody>
</table>
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