Women with Epilepsy in Reproductive Age Group: Special Issues and Management Strategies

Shehanaaz Begum*, Sanjeev V Thomas**

Abstract

Women with epilepsy (WWE) have several gender based problems pertaining to social and biological domains. The stigma of epilepsy and its consequences appear to be more for women than men. They have more difficulty in getting married and sustaining a married life. The cyclical variations in the reproductive hormones can adversely impact the seizure pattern in WWE. Epileptiform discharges in the brain can influence the hypothalamic functions and lead to sexual dysfunction. The Antiepileptic drugs (AED) may alter their metabolic and hormone profile and contribute to this disorder. Most WWE tend to have uneventful pregnancies and healthy babies. Nevertheless, the risk of fetal malformations appears to be increased when AEDs are used during pregnancy. This risk is higher for those who are on polytherapy, or using valproate. Recent studies have also demonstrated that antenatal exposure to AEDs could lead to neurocognitive and developmental impairment, low IQ or language problems in exposed infants. Clinicians need to consider these special issues while initiating AED therapy in adolescent girls. All WWE need to have a detailed pre conception evaluation wherein the need to continue AEDs, the ideal AED and dosage are reassessed. The AED therapy would have to be individualized according to the clinical situations, obstetric background and family concerns. Folic acid should be prescribed to all women who could potentially become pregnant. Detailed screening for fetal malformations by estimation of serum alpha fetoprotein and fetal ultrasonography need to be carried out between 14 -18 weeks of pregnancy. The dosage of AEDs may have to be escalated in the second half of pregnancy in selected patients. The family should be provided detailed counseling and information on how to cope with the pregnancy, childbirth, lactation, and contraception.

Introduction

It is estimated that about 50 million people worldwide have epilepsy and women constitute half of this number. In India, about 5.5 million people have epilepsy. 2.5 million of them are women and 1.3 million of these women with epilepsy (WWE) belong to the reproductive age group.

There is significant gender based difference in the biological, pharmacological, psycho social and economical profile of epilepsy. The biological variations are attributed to the influence of female reproductive hormones on epileptogenesis and seizure recurrence. Seizure exacerbations with menarche and menopause and catamenial worsening are examples. WWE also suffer a more severe psycho social impact when compared to men with epilepsy. Continuous use of AEDs can increase the risk of sexual dysfunction, infertility and fetal malformations.

Most of the recent literature regarding WWE and their reproductive problems has come from the various epilepsy and pregnancy registries. Worldwide, there are 5 registries which follow up WWE.

Social issues in WWE

Unlike others, the European registry and the UK registry do not include WWE who are not taking any AEDs. KREP, EURAP and the Australian registry collect data from the maximum number of contacts. Of these, the Australian registry collects data over telephone. They also differ in their duration of follow up, outcome ascertainment methods, outcome classification, control selection methods etc. Among the five, KREP is the only one providing pre conceptional counseling. Under KREP, WWE and their children are followed up to the age of 12yrs.

KREP has an important role in the Indian scenario as it is generating data from our country. The genetic constitution, socio economic environment and health care delivery system that would influence the foetal and maternal outcome for persons with epilepsy are different in different populations. The final outcome of the disease and the effect of AEDs in different populations may vary based on many such factors. For example, the US registry has found an increase in the incidence of cleft lip and palate in their population while the UK or European registries have not.

Table 1: Characteristics of various epilepsy and pregnancy registries

<table>
<thead>
<tr>
<th>Year of commencing</th>
<th>Pre conceptional evaluation</th>
<th>Includes those not on AED</th>
<th>Exclusion criteria</th>
<th>Data collection</th>
<th>Malformation ascertainment at</th>
<th>Control selection</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>1996</td>
<td>No</td>
<td>AED change</td>
<td>2 contacts</td>
<td>&lt;12 wks</td>
<td>Internal</td>
<td>2000</td>
</tr>
<tr>
<td>US</td>
<td>1997</td>
<td>No</td>
<td></td>
<td>3 contacts</td>
<td>&lt;12 wks</td>
<td>External</td>
<td>No</td>
</tr>
<tr>
<td>KREP</td>
<td>1998</td>
<td>Yes</td>
<td></td>
<td>4 contacts</td>
<td>12 months</td>
<td>External</td>
<td>No</td>
</tr>
<tr>
<td>EURAP</td>
<td>1999</td>
<td>Yes</td>
<td></td>
<td>4 contacts</td>
<td>12 months</td>
<td>Internal</td>
<td>No</td>
</tr>
<tr>
<td>Australia</td>
<td>2000</td>
<td>Yes</td>
<td>AED change</td>
<td>4 contacts</td>
<td>12 months</td>
<td>Internal</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Abbreviations: UK, United Kingdom; US, United States; KREP, Kerala Registry of Epilepsy and Pregnancy; EURAP = An International Registry of Antiepileptic Drugs in Pregnancy; AED, Anti-epileptic Drug**

In a comparison of young men and women with JME (Juvenile Myoclonic Epilepsy) or TLE (Temporal Lobe Epilepsy) living in India, it was found that there were significant gender based differences in the profile of epilepsy. WWE were found to have...
higher odds ratio for remaining unmarried (OR 2.81) than men (OR 1.63) across all age groups from 20-44yrs. WWE were also observed to have higher rates of unemployment and divorce.4

**Infertility**

Issues regarding reproduction are a major concern in WWE. Earlier studies have indicated that WWE have reduced fertility.5 Infertility is defined as the inability to conceive even after 12 months of unprotected intercourse. A prospective study over 10 years under KREP had shown that WWE have a greater risk for infertility, especially with polytherapy.6 The prevalence of infertility among WWE was more than double (38.4%) that among women in the general population (15.15%). Also, the WWE who conceived had a fewer number of children than the rest. Infertility was least for those who were not on any AEDs (7.1%) while it was 31.8% for those taking one AED, 40.7% for those taking two AEDs and 60.3% for those taking three or more AEDs. Those exposed to Phenobarbital had a significant risk of infertility (OR 1.517 for monotherapy and OR 1.43 for polytherapy) but no such trend was observed with valproate or other drugs in that study.6

**Effect of Pregnancy on Epilepsy**

Another concern is the recurrence of seizures during pregnancy. In general, 20-30% of WWE may have exacerbation of seizures during pregnancy, 20-30% show improvement and 40-50% experience no change in seizure pattern.7 The cause for seizure recurrence varies with the stage of pregnancy. In the first trimester recurrence is mostly due to mental stress, sleep deprivation, hormonal changes etc. Patients may be apprehensive about the adverse effects of AEDs on the fetus and may tend to discontinue treatment. Another issue is hyperemesis which indirectly results in drug default. Either ways non compliance is a major cause of seizure recurrence in pregnancy. During the second and third trimesters there is significant hemodilution which causes a reduction in the blood levels of AEDs. This compounded with increased elimination of drugs, especially lamotrigine and oxcarbazepine and to some extend levetiracetam can result in breakthrough seizures. Therefore patients on these AEDs can be prescribed to take an increased dose of the same.

Of the 1,297 pregnancies in WWE enrolled in KREP, all the three patterns were observed. 47.8% remained seizure free during pregnancy. Seizure relapse was highest during the three peripartum days. Recurrence was more with localization related epilepsy (LRE) than generalized epilepsy (OR 1.6, CI 1.2-2.0). Also, patients with poor seizure control in the pre pregnant month were more likely to have seizure recurrence in pregnancy when compared to those with seizure free pre pregnant period. Polytherapy was significantly associated with seizure relapse than monotherapy.8

**Effect of Epilepsy on Pregnancy**

There is no undue risk of pregnancy and childbirth in WWE.5-11 WWE are found to have an adverse maternal outcome of pregnancy. In a prospective study9 where the complications of 643 completed pregnancies were compared with 18,272 pregnancies managed in a teaching hospital, it was found that WWE had a higher chance for some complications like, anemia, ovarian cyst, fibroid uterus, spontaneous abortions and seizures in the peripartum period. The risk of caesarean section was not increased in WWE.

**Teratogenic Effects**

Ante natal use of AEDs has been associated with increased risk of fetal malformations. Various mechanisms have been proposed as to how AEDs exert their teratogenic effects.12 AEDs may lead to folate deficiency and thus predispose to neural tube defects. AEDs that are metabolized by cytochrome P450 enzymes in the liver increase the levels of arene oxide which is a byproduct of this metabolism. Arene oxide is a potent teratogen. Other mechanisms include alteration of homeobox (HOX) genes, retinoic acid signaling pathway, histone deacetylators, polymorphisms involving AED transporters and oxidative stress.13,14

Considerable amount of data has come from the various registries regarding fetal malformations.2,15-17 But it is important to consider the characteristics of the registry, their selection criteria, case ascertainment methods and follow up duration while interpreting their results.

Under KREP, malformations are defined as serious defects which interfere with the quality of life unless they are managed. Others which produce only a cosmetic effect and do not interfere with the quality of life are considered as anomalies and do not qualify as major malformations.

AEDs can induce malformations in almost all organs. These can be broadly classified into cardiac malformations (tetralogy of Fallot, atrial septal defect, ventricular septal defect, patent ductus arteriosus, pulmonary atresia, single ventricle etc.), malformations of the nervous system (neural tube defects), skeletal defects (club foot, hip dislocation etc.), cranio facial defects (cleft lip and palate), malformations of the gastro intestinal system (esophageal atresia, congenital hypertrophic pyloric stenosis, inguinal, diaphragmatic and umbilical hernias and omphalocele), malformations of the genitor urinary system (renal agenesis, hydrenephrosis, hypospadias and undescended testis) and malformations involving multiple systems. In a prospective study from the UK epilepsy and pregnancy register, 4.2% of live births to WWE had major congenital malformations. The rate of major congenital malformation was more with polytherapy than monotherapy (adjusted OR 1.83).18 In a larger study involving patients from Europe, Australia and India, it was observed that there was a dose dependent increase in the risk of malformations for carbamazepine, lamotrigine, valproate, and Phenobarbital.2

**Long Term Outcome**

Until recently, not much research was directed to the adverse effects of AEDs on the long term language and IQ development of children exposed to AEDs in utero. A long term adverse effect of ante natal use of AEDs is impaired neurocognitive development in infants exposed to AEDs prenatally. A prospective evaluation of 15 month old infants of mothers with epilepsy enrolled in KREP showed that about one third of them had a significantly impaired mental (MeDQ) and motor (MoDQ) development quotient. Those exposed to polytherapy had a significantly lower development quotient than those exposed to monotherapy. Valproate monotherapy was associated with significantly lower MeDQ and MoDQ when compared to carbamazepine.18

In a follow up study under KREP where children of mothers with epilepsy, of age 6 years and above were compared against age and socio economic status matched controls, it was found that the test group scored significantly less than the controls in both full scale IQ test (FSIQ) and language test. It was also observed that children with low MeDQ and MoDQ at one year of age continued to have low FSIQ and MLT at 6 years of age.
(p value 0.05, 0.05 and 0.02 respectively). Also the polytherapy group had lower mean FSIQ than monotherapy group. Those exposed to higher cumulative load of AEDs had significantly lower FSIQ and MLT scores compared to those exposed to lower drug load.19 The findings were later confirmed in a sample drawn from UK and USA as well as Europe.20,21

Management Approach

The AED therapy in adolescent girls should ideally be tailored considering their reproductive needs. WWE should be advised to consult their neurologist before starting a family. Their diagnosis should be actively re-assessed at this point of time (Figure 1). It is not rare to find women who are inadvertently started on AEDs for non epileptic conditions misdiagnosed as epilepsy. Some are found to be in remission and in them drugs may be withdrawn following the general principles. However, the risk of recurrence of seizures, particularly with the risk of marriage and its impact needs to be addressed. Patients with Juvenile Myoclonic Epilepsy need to be continued on AEDs as they are at high risk of seizure relapse on complete withdrawal. Any changes in the pattern of drug therapy may be planned prior to pregnancy. Reduction of doses, change over to less teratogenic drugs and conversion of polytherapy to monotherapy may be done depending on the disease status of individuals. Pre pregnancy blood levels of AEDs can also be checked.22,23

WWE who are likely to get pregnant may be started on folic acid 5mg/day pre conceptionally. WWE and their families may be counseled regarding the need to continue AEDs in order to remain seizure free, that >90% of infants born to WWE on AEDs are healthy, the risk of a major malformation is 6-8% and that this is seen mostly with WWE taking polytherapy and high doses of AEDs. The need to take folic acid daily has to be reinforced.

Under KREP, pregnant WWE are screened for malformations at 16-18 weeks of pregnancy with serum alpha feto protein levels at 16 weeks as well as a fetal ultra sonogram at 18 weeks of pregnancy (Figure 2). This provides a margin of 2 weeks time for a safe termination before 20 weeks in the event of a malformation. Malformation focused ultrasonography can be done as early as 12 weeks. But it has been found that the expertise regarding malformation detection with an early scan is highly variable among radiologists and in some instances may not be helpful. Therefore an ultra sonogram at 18 weeks is preferred. In the second trimester blood levels of AEDs tend to fall due to hemodilution and other metabolic changes. Periodic monitoring of blood levels especially free blood levels in first, second and third trimesters can guide the physicians in adjusting the dosage of AEDs. Anticipatory increase of AED dose may be done with lamotrigine and oxcarbazepine as their blood levels fall significantly and in most instances lead to breakthrough seizures. With other AEDs, dose is usually increased only if breakthrough seizures occur as most of the WWE go through their second and third trimesters uneventfully even with pre pregnant doses.

We advise all WWE to take two doses of vitamin K 10mg IM at 34 and 36 weeks of pregnancy respectively as vitamin K tablets are not available in India. This is to prevent hemorrhagic disease of the newborn. Mode of delivery is generally dictated by the obstetric needs. Routine doses of AEDs must be administered to the lady in the labor room also. If she has an increased propensity to develop seizures an elective caesarean section may be performed.

Post partum Management

The necessity of contraception and birth spacing in WWE cannot be over emphasized. Oral contraceptives are generally avoided in those taking enzyme inducing AEDs for fear of failure. But if the couple prefers oral contraceptive pills, high estrogen pills may be prescribed, i.e. pills containing ≥ 50µg of estrogen. Medroxy Progesterone Acetate depot injection once
every 3 months is another alternative. In an Indian setting, intra-uterine contraceptive devices are generally preferred.

Child rearing is a physically and emotionally demanding task as far as WWE are concerned. Hence they have to be prepared for this. It is generally seen that WWE either refrain from or are not given an opportunity to look after their infants due to multiple reasons. Upbringing of these children by others may interfere with their development. Therefore, maternal involvement in child rearing has to be fostered. WWE often skip medications or refrain from breast feeding for fear of AEDs finding their way into breast milk. But only traces of AEDs are found to pass into breast milk. This exposure is not demonstrated to produce any significant adverse effects in children. According to a recent prospective study no significant difference has been found between children of WWE exposed to AEDs via breast milk and those with no such exposure regarding IQ at 3 years of age. There are only anecdotal reports of adverse effects of AEDs in breast fed babies. Moreover, the benefits of breast feeding far outweigh the adverse effects and needs to be fostered. It is recommended that mothers first nurse their babies and then take medicines so that blood levels will not be very high during breast feeding. Sleep deprivation for nursing the child at night may lead to break through seizures especially in those with Juvenile Myoclonic Epilepsy. In such cases family members should be adequately counseled and compliance ensured. Mothers can use expressed breast milk during night. Good compliance to AEDs and compensatory sleep during daytime needs emphasis in them. WWE are advised to nurse their babies in such a way that in the event of a seizure she may not drop the baby or fall over and suffocate it.

Conclusion

Management of epilepsy in women of child bearing age involves close interaction between the clinician, patient and family members. Most women can expect safe pregnancy and healthy babies. Careful planning of pregnancy, folate administration, optimization of AED therapy, close monitoring and screening for fetal malformations are very important. Neurologist, obstetrician and a neonatologist need to work as a team to offer the best medical care for women with epilepsy and their children.

Reference

2. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers H, et al. h olmes LB, Baldwin EJ, Smith cr, habecker E, glassman L, Wong