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Review Article
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Pregnant Women with Epilepsy: Management Issues

Bhanu Priya[1] and Nilanchali Singh[2]*

[1]Department of Obstetrics and Gynaecology, University College of Medical Sciences, India
[2]Department of Obstetrics and Gynaecology, Maulana Azad Medical College, India

Abstract

Epilepsy is one of the common neurological disorders complicating pregnancy with a prevalence of 0.5-1%. Epilepsy seizures are characterized by paroxysmal cerebral dysrhythmias. Epilepsy in pregnancy (EIP) is challenging to both obstetricians and to neurologist. Pregnancy alters the natural history of epilepsy and seizure episodes are likely to worse. Obstetricians also face challenges of increased risk of teratogenicity while women on anti epilepsy drugs (AED). Epilepsy in pregnancy in Indian scenario also has both social and gender related issues. This review has been designed to address the management of women with epilepsy (WWE). Also, there will be particular stress on the recommendation regarding issues of pregnancy including antenatal and intrapartum care, preconceptional counselling and information regarding teratogenicity of AED and drug monitoring and its optimization.

Keywords: Epilepsy; pregnancy; Obstetricians; Drug monitoring

Pregnancy Care

WWE has multiple issues in the antenatal, intrapartum and postpartum period. Epilepsy is likely to affect the seizure frequency, risk of teratogenicity and obstetric outcome [1]. It is a special situation of pregnancy as it can be confused with Non proteinuric hypertension and there are also conflicting report of increased chances of abruptio placentae and pre eclampsia and eclampsia in WWE [2].

Epilepsy behavior in pregnancy and vice versa

Pregnancy behaves unpredictably on seizure frequency. Classically said, rise in estrogen and progesterone in pregnancy increase the neuronal excitability, hence, lowers the seizure threshold. Majority of women (66.6%) remained seizure free throughout the pregnancy and Generalized tonic-clonic seizures (GTCS) occurred in 15.2% of the pregnancies [3]. The EURAP registry reported, using first trimester as reference, seizure control remained unchanged throughout pregnancy in 63.6%, 92.7% of whom were seizure-free during the entire pregnancy. For those with a change in seizure frequency, 17.3% had an increase and 15.9% a decrease [4]. Seizure control prior to the pregnancy is a good predictor of seizure control during pregnancy. A study done by Vajda et al. in 2008 observed little impact on seizure frequency in WWE on AED. A seizure free interval of one year cause 50-70% reduction in seizure frequency [5].

Significant impact of epilepsy has been observed over the obstetric outcome. A meta analysis done between a period of 1990-2015 observed increased odds of spontaneous miscarriage (OR 1·54, 95% CI 1.02-2.32), antepartum haemorrhage (1.49, 1.01-2.20), post-partum haemorrhage (1.29, 1.13-1.49), hypertensive disorders (1.37, 1.21-1.55), induction of labour (1.67, 1.31-2.11), caesarean section (1.40, 1.23-1.58), any preterm birth (<37 weeks of gestation, 1.16, 1.01-1.34) and fetal growth restriction (1.26, 1.20-1.33) when compared with women without epilepsy. The odds of early preterm birth, gestational diabetes, fetal death or stillbirth, perinatal death or admission to neonatal intensive care unit did not differ between women with epilepsy and those without the disorder [6].

Epilepsy related mortality is not so uncommon entity and the subject is still under research. The risk of death is ten folds in WWE than women without the condition [1]. A United Kingdom based research observed, 0.6% or 13,978 were WWE out of 2,291,493 maternities. Fourteen deaths were epilepsy-related, of which 11 (79%) were sudden and unexpected (SUDEP). Nine occurred during pregnancy and five were postpartum [1]. Another retrospective study conducted by Macdonald et al. in 2015 observed a risk of death in WWE during delivery hospitalization was 80 per 1,00,000 pregnancies and was statistically higher than 6 deaths per 1,00,000 pregnancies in women without epilepsy (adjusted OR 11.46) [7].

On the contrary, fetus is relatively resistant to small degree of hypoxia occurring while seizures episode but prolonged hypoxia occurring during status epilepticus can result in sustained fetal hypoxia. EURAP registry 2013 reported status epilepticus in 0.6% (2/3806) of all pregnancies and observed only one perinatal death which eliminates the prior belief of having poor outcome with status epilepticus. This improved outcome suggests better maternal care and lower threshold for delivery.

AED levels and dose optimization

Pharmacokinetics is significantly altered in pregnancy as changes occur in body weight, drug absorption, protein binding, metabolism and excretion of drug, hence, the levels of most of the drugs. As the serum protein level fall, serum concentration of AED that is total drug concentration falls, but the unbound concentration remains stable. The relatively newer AEDs like lamotrigine, oxcarbazepine as well as levetiracetam noted clinically significant reduction in plasma concentration [8-10]. Lamotrigine levels can fall as low as 70% in pregnancy [11]. There is a controversy whether the AED levels should be measured or clinical monitoring should be done. There are no set guidelines as no direct comparisons have been done between regular therapeutic monitoring or clinical monitoring.

In WWE, the aim of therapy is to maintain seizure control with

***Corresponding author:** Nilanchali Singh, Assistant Professor, Department of Obstetrics and Gynaecology, Maulana Azad Medical College, Delhi, India, Tel: +919811343168; E-mail: nilanchalisingh@gmail.com

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lowest AED dosage. So, clinicians should decide for therapeutic drug monitoring if there is suspicion of non adherence, toxicity and uncontrolled seizures.

Monitoring of birth defects

WWE on AED have relatively higher chances of congenital malformations (CM) than general population (2-3%) [12,13]. The WWE not on AED have same risk as of general population. Screening of birth defects should be offered to the couple at 11-13 weeks by early anomaly scan to detect acrania (early stage of anencephaly) and increased nuchal translucency for ruling out cardiac and other defects [14]. At mid trimester (18-20 weeks) detailed targeted scan for CM should be done with special emphasis on heart, neural tube and face. Biochemical screening by maternal serum alfa feto protein (MSAFP) along with ultrasound increases detection rate of neural tube defects to 94-100%. No study has separately recommended for fetal echocardiography apart from the 20 week detailed scan.

Monitoring of WWE in pregnancy

Antenatal period should be regularly assessed for women's wellness, ability to cope, memory, concentration and sleep, tiredness and dizziness. The AED being taken or missed, dosing schedule, dose, seizure type, frequency and auras should be inquired about. Any precipitating factor like fasting, stress, sleep deprivation should be identified and treated. In WWE with active seizures, minimal time the women should left unattended and unobserved. Individual with unwitnessed seizures are at likely of SUDEP. Early discussion should be done with neurologist if there is poor seizure control and any required dose adjustment should be done.

Vitamin K supplementation

Prenatal vitamin K supplementation in late third trimester has been an issue of controversy. It was proposed enzyme inducing AED (EIAED) competitively inhibits precursor of clotting factors and affect fetal microsomal enzymes that degrade Vit K thereby increasing the risk of Early hemorrhagic disease of newborn. But, several case control studies observed no increase in neonatal bleeding born to women taking EIAED [15]. On the basis of these studies only NICE has recommended against the prenatal administration of Vit K. However, 1 mg I.M Vit K is routinely given to the neonate after birth. Vitamin K administration in late pregnancy to prevent post partum hemorrhage is still a matter of discussion till now and no studies are available.

Intrapartum Care

The risk of seizures during labor is low provided adequate analgesia and appropriate care of labor is given to minimize the risk factors like insomnia, stress and dehydration. EURAP registry observed 3.5% incidence of seizures of WWE in labor [4]. Hence, the delivery should be conducted in a center where appropriate facilities for maternal and neonatal resuscitation is available. Epilepsy is no contraindication for normal vaginal delivery and early delivery is also not indicated. There is also no evidence of AED affecting labor inducing agents. WWE should continue her AED and good intravenous line should be secured. Seizures precipitating factors like pain, hyperventilation, stress, dehydration should be avoided. Continuous CTG monitoring is recommended in an event of seizures or women high risk of seizures in labor. Seizures during labor should be terminated at earliest to prevent maternal and fetal hypoxia. Benzodiazepines are the drug of choice for seizures in labor.

Postpartum Care

The peripartum period especially, 3 days peripartum has shown maximal seizure exacerbation. The risk is highest in women who had seizures in a month prior to pregnancy compared with those who were seizure free during same period (OR 3.7) [16]. Neurological consultation should be sought within 10 days for any alteration in any drug dosing as maternal drug levels can fluctuate. If doses during pregnancy were increased, toxicity can occur as AED demand decreases.

WWE are also at increased risk of postpartum depression as compared to women without epilepsy (29% versus 11% in control) [17]. All AEDs are secreted in breast milk. Newer AEDs are secreted more than the older ones. Newer generation drug like lamotrigine, levetiracetam, oxcarbazepine should be recommended for breast feeding only when benefits outweigh the risk. Further data is required to establish the safety of newer drugs.

Individualized approach for monitoring of withdrawal symptoms and toxicity should be used especially in premature babies. Breastfeeding has not shown any cognitive changes at 3 years of age in children exposed to lamotrigine, valproate, phenytoin or carbamazepine monotherapy.

The safety of mother and neonate at home is another issue that needs to be addressed at the time of discharge. Safety strategies include nursing baby on floor, shallow bath and bathing should not be unattended and avoid risk factors for seizures and use of another help. Lastly, family and social support is not an overemphasized fact.

Contraception

Contraceptive advice is challenging in case of WWE. It prevents unplanned pregnancies and unnecessary stress. The efficacy of hormonal contraception is going to be reduced in women taking EIAED like phenytoin, carbamazepine, oxcarbazepine, topiramate. EIAED induce hepatic enzymes and increase excretion of drug [18,19]. Also, the level of sex hormone binding globulin (SHBG) are increased which decreases free level of circulating hormone [19]. The non enzyme inducing AEDs like valproate, benzodiazepines, gabapentin, pregabalin, levetiracetam, tigabine and vigabatrin do not alter hormonal contraception efficacy [19].

EIAEDs cause increased metabolism of estrogen and progestogens in COC pills. Contraceptive alternatives like depot medroxyprogesterone acetate (DMPA), levonorgestrel releasing intrauterine contraceptive device (Mirena) or barrier methods are considerably safe in women taking EIAEDs [20,21]. Traditionally, higher doses of COCs were prescribed (50 mcg ethinyl estradiol) [22,23]. Whereas now, the studies have revealed that increase in progestin is also required for ovulation suppression. Hence, the recommendation is to increase both progestin and estrogen. Tricyclic pills with shorten pill free interval are also recommended for further efficacy [20]. Barrier contraception should be used add on to COCs for better results [24]. Recent studies suggest that consumption of combined oral contraceptives (COC) increases lamotrigine metabolism by increasing glucoronidation and reducing the level by 50% and worsening the seizure control [18,21,25]. Hence, increment in dose of lamotrigine is required while women on COC.

Levonorgestrel implants like Norplant and implanon have observed lower levonorgestrel levels in women taking EIAEDs and subsequent higher failure rates have been reported [26,27]. Despite failure of subcutaneous progestin implants, high dose of DMPA provide effective contraception in women taking EIAEDs. Additionally, DMPA has been shown to reduce the frequency of seizure episodes [19]. The

levonorgestrel releasing intrauterine device (mirena) is considered to be the first line contraceptive method for WWE taking EIAEDs. It acts locally and it has very low failure rate of 1% in the women [28]. The recommended emergency contraception for women taking EIAEDs is copper intrauterine device. Other emergency contraception like levonorgestrel or ulipristal acetate pills are not effective as their levels get altered [24]. Hence, effective contraception is required for stabilization of epilepsy and to optimize the outcome of pregnancy.

Preconception Counselling

Preconceptional counselling is a must in WWE as the disease has effect on pregnancy and vice versa. The special importance should be given on reproductive dysfunction and subfertility affecting reproductive outcomes. The pregnancy itself is a high risk state for epilepsy, hence, optimizing the dose of AEDs before planning pregnancy is necessary. The women should also be discussed about teratogenic effect of AED and folic acid supplementation and also the delayed neurocognitive changes in child.

Reproductive dysfunction and subfertility

Reproductive dysfunction and subfertility are two to three times more common than general population [29]. Seizure activity leads to increased serum prolactin levels in WWE [30]. Menstrual abnormalities in 50% and higher rates of anovulatory cycles are reported in WWE. The prevalence of polycystic ovarian disorder (PCOD) is also higher which is 41% [31,32]. Reduction in libido has also been reported in one third of women. Women on AED also have reproductive and endocrine disorders. AED affects hypothalamus pituitary ovarian axis, EIAED increase SHBG results in fall in biologically active estradiol and testosterone. Valproic acid is associated with increased rate of hyperandrogenism, PCOD and ovulatory dysfunction especially in young women [32].

However, these observations are not so classical, as earlier said, as it did not match in any of the study. A recent Scandavian study suggested that the results are relatively modest. The birth rate was lower in WWE than women without epilepsy [33].

Optimizing AEDs for pregnancy

Preconceptional counseling regarding effect of AED over pregnancy is an essential issue. Teratogenic risks are the most important concerns of AED, but the benefit of stopping or continuing or changing the AED should be weighed against the risk of developing seizures. There are lot of variation between risk of malformation and the different AEDs when used as monotherapy. The general guidelines to stop the AEDs are also followed here. Women with a seizure free interval of 2-5 years (well controlled) are eligible candidate for reducing or switching to monotherapy or stopping the drug. The risk of seizure relapse is low in women with normal IQ, EEG and neuroimaging pattern. Women with juvenile myoclonic epilepsy is one of the exception where AEDs should continue despite seizure free interval as it has higher relapse rate [34]. In brief, the teratogenic risk depends on type number and dosage of AED.

Genetic counselling should be offered to women with a risk of inheritance or if both partner have epilepsy. Women should be counselled about increased risk of teratogenicity if there is previous history of congenital malformations (CM) [35].

The risk of CM by AEDs can also be minimized by folic acid supplementation. There are no set guidelines for dosage of folic acid. American academy of Neurology and American epilepsy society recommend 0.4 mg/day but NICE recommend 5 mg/day [36,37]. This is left to physicians discretion to treat the women.a definite association has been seen with risk of CM in women with no or low folate levels [37,38].

The main target before planning pregnancy remains that women should be on minimal and least teratogenic drug and at least 12 month seizure free [5,39,40].

Teratogenic effects of epilepsy and AEDs

The major concern with epilepsy is CM which is higher in WWE due to AEDs. Women taking AEDs have a 4-14% chance of CM as compared to 2-3% n the general population [41]. Per se, WWE not exposed to AEDs, have a similar incidence of CM as in general population [42]. Risk of CM is dose dependent, but this has been demonstrated in valproate only [43]. Also, in polytherapy, the CM risk are associated with drug combinations that were not documented when each individual drug was used as monotherapy [44]. The variation of risk increases to 17% when AEDs are used as polytherapy [45,46].

There are many unresolved queries about pregnancy and effect of AED. Until recently, it was stated that newer generation AED are as effective as older ones. But, no consolidated data is available on efficacy of these drugs in pregnancy. The risk estimation of CM is incomplete due to confounders like type of epilepsy, family history, exposure to additional teratogenic agent. There is no consensus on minor anomalies and effect of AED on long term neuro cognitive behavior. Hence, the formation of AEDs registries has solved this problem and provided a large scale systematic data. There are different types of registries, independent academic registries, pharmaceutical drug registries and population based registries. The European and International registry of Anti epileptic drugs and Pregnancy (EURAP) is independent registry. It includes 42 countries of Europe, Asia, Oceania and South America [47].

The North American Anti epileptic drug pregnancy registry, the United Kingdom Epilepsy and Pregnancy group and Australian pregnancy registry and Kerala pregnancy registry are also independent academic registries [48-50]. The Australian and Kerala registries have recently merged into EURAP. The pharmaceutical registries are, the Glaxosmithkline's International Lamotrigine Pregnancy Registry and recently launched UCB AED Registry [51].

While these ED registries provide most consolidated data on CM risks, there are certain limitations also. There are methodological differences among the different registries. It is calculated that study over approximately 500 AED monotherapy is needed to confidently identify differences in CM between AEDs [52].

The risk for spina bifida for carbamazepine monotherapy (OR 2.6, 95% CI1.2-5.3) when compared with no AED exposure [53]. The Major CM rates for lamotrigine exposure was 3.2% (95% CI 2.1-4.9) [54]. The teratogenic effects of levetiracetam are virtually unknown. UK Epilepsy and Pregnancy Registry 2006 failed to find CM in their 39 women on levetiracetam monotherapy [55]. However, Holmes et al. revealed 2.03% CM rates on levetiracetam monotherapy [56]. Meador et al. observed a 4.9% CM rates with phenobarbital [52]. Phenytoin is associated with fetal hydantoin syndrome, comprising of hypoplasia and irregular ossification of distal phalynx, facial dysmorphism, epicanthal folds, hypertelorism, broad nasal bridge and mental retardation. Hanson et al. reported 11% prevalence of fetal hydantion syndrome and additionally, 30%, when in utero exposure [57]. Hunt et al. reported a cm rate of 4.8% (95% CI 1.7-13.3) on topiramate exposure, which almost tripled

AED	Risk in Percentage (95% confidence interval)
Carbamazepine	
Morrow et al. [55]	2.2% (1.4-3.4)
Meador et al. [60]	4.6%
Holmes et al. [48]	2.6%
Phenytoin	
Hanson et al. [57]	11%
Valproic acid	
Meador et al. [52]	10.7% (8.16-13.29)
North American pregnancy registry [61]	10.7%
UK pregnancy registry [61]	6.2%
Neurodevelopmental effect of antiepileptic drugs study group [63]	20.3% (CM+fetal death)
Phenobarbital	
Meador et al. [52]	4.9%
Lamotrigine	
Morrow et al. [55]	3.2% (2.1-4.9)
Holmes et al. [61]	10.4% (4.3-24.9)
Levetiracetam	
Vajda et al. [62]	2.4%
Holmes et al. [56]	2.03%
Topiramate	
Hunt et al. [58]	4.8% (1.7-13.3)
Holmes et al. [56]	4.1% (1.9-6.1)
Gabapentin	
Morrow et al. [55]	3.2% (0.6-16.2%)

Table 1: Risk of major congenital malformations with AED monotherapy.

to 11.2% (95% CI 6.7-18.2) when used in polytherapy [58]. Valproic acid cause dose dependent teratogenicity. Meador et al. observed 10.7% (95% CI 8.16-13.29) risk of CM involving multiple organ system. When AEDs used as polytherapy the CM risk ranges from 19.8-6.0% versus 3.7% in monotherapy [59-65] (Table 1).

The decision of AED for women planning to get pregnant should be made cautiously and decision for dose, drug selection and management should be discussed with WWE.

Neurocognitive effects

There has been rising concerns about neurocognitive effects of AED apart from its structural effects. A 2014 Cochrane database reviewed that there were no significant differences in the developmental quotient of children exposed to AEDs, carbamazepine, lamotrigine, phenytoin [66]. However, children exposed to valproate had significantly lower motor and mental developmental quotient of infants of WWE at mean age of 15 months. Higher doses of valproate are associated with poor verbal ability, low IQ, poor memory and executive function [67]. Levetiracetam is not associated with cognitive disabilities but the study are few and more research is needed [68].

Overall, valproate is the drug which has major teratogenic side effects with neurocognitive effects. Since, the data is still emerging and more and more study are upcoming, hence, the confounders should be taken care of like, seizure frequency, type of epilepsy, genetic factor and parental cognitive functions.

Conclusion

WWE is a common neurological disorder and can be dealt by multidisciplinary approach. Pregnant WWE should have ultrasound for detection of fetal anomalies, adequate screening for obstetric complications. The AEDs should be optimized for pregnancy related changes and if required, drug monitoring can also be offered. During delivery, all stress factors should be allayed and seizure protocol should be maintained. The discharge of women should be planned only after AED drug and dosage optimization and with proper instruction to WWE for newborn care. This also includes contraceptive counseling. Most women have good maternal outcome but pre pregnancy counseling is necessary to optimize god maternal and fetal outcome. This includes improving fertility and decreasing sexual dysfunction, optimize AED for next pregnancy. Women should be counseled about teratogenic side effects and dose optimization and about effects of AED over infants.

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