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Review Article

Management of Epilepsy and Pregnancy

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Abstract

There are one and half million women with epilepsy (WWE) in India. Registry based prospective data indicate that most women with epilepsy have uncomplicated pregnancy and give birth to healthy babies. The risk of major malformations may be increased by 1.5 -3 times when WWE use antiepileptic drugs. All antiepileptic drugs carry the risk of fetal malformation, but Sodium valproate particularly at doses higher than 1000 mg can be harmful. It is important that WWE plan pregnancy and consult their neurologists in advance. AEDs can be stopped or reduced considerably in several WWE before pregnancy. They need to undergo screening for fetal malformations before 20 weeks of pregnancy. Some WWE may require adjustment of AED doses to maintain seizure freedom. Pregnancy in WWE needs to be closely monitored by gynecologists and the babies followed up carefully.

Key words : Epilepsy, pregnancy, antiepileptic drugs, (AED) teratogenic effect, malformation

Introduction

It is estimated that there are over 1.5 million women with epilepsy in reproductive age group in India. People with epilepsy, especially women, experience tremendous social stigma and alienation in life. Women With Epilepsy (WWE), in the childbearing age group, have fewer children than age matched controls [1]. Neurologists and gynecologists who are increasingly faced with WWE during pregnancy are not adequately informed about their optimal management [2]. There are several important aspects to managing pregnancy in WWE. Pregnancy influences the natural history of epilepsy and seizures are likely to worsen in about a third of them. The bioavailability of Anti Epileptic Drugs (AEDs) may change considerably due to alterations in its pharmacodynamics and kinetics. Most importantly, most AEDs are potentially teratogenic and may increase the risk of fetal malformations. The complex interaction between epilepsy and pregnancy is traditionally discussed under three headings viz. effect of pregnancy on epilepsy, effect of epilepsy on pregnancy and effect of epilepsy and AEDs on fetus. The purpose of this article is to review the recent concepts in optimal management of pregnancy in WWE.

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Effect of Pregnancy on Epilepsy

Several experimental and clinical studies have shown that seizures are influenced by the female sex hormones - estrogen and progesterone [3,4]. In general, estrogen lowers the seizure threshold and progesterone elevates it. Conjugated estrogen, when administered intravenously, activated epileptiform discharges in 11

of 16 women with clinical seizures [5]. In another study, four of seven women with partial epilepsy showed significant reduction in interictal spike frequency when progesterone was infused intravenously [6].

Seizures can occur during pregnancy and postpartum period for several reasons but epilepsy is probably the most common cause. Occasionally other causes such as metabolic derangement, eclampsia and cerebral venous sinus thrombosis may cause seizures during pregnancy. These conditions are classified as special syndromes according to the recent classification of epileptic syndromes [7]. Recurrent seizures without any provoking factors only come under the category of epilepsies. Seizures would have started before pregnancy in most instances. Rarely some women may experience seizures only during pregnancy, which is termed gestational epilepsy. Such women would be seizure free in between pregnancies. Another subgroup (gestational onset epilepsy) may have their first seizure during pregnancy and thereafter may continue to get spontaneous recurrent seizures. About 1-2 percent of WWE may experience status epilepticus (SE) during pregnancy, which is associated with high morbidity and mortality [8].

Effect of pregnancy on seizure frequency

Pregnancy has variable effect on seizure frequency. Seizure frequency may remain unchanged or decrease in two third of WWE while it may increase in others [9]. About 1% of them can have SE.

Diverse mechanisms have been put forward to explain the change in seizure frequency during pregnancy. Apart from the variation in reproductive hormones, several other factors such as non-compliance and decrease in blood levels of free form of AED influence seizures during pregnancy. (Table 1)

Table 1.Possible causes of increase in seizure frequency during pregnancy.

Hormonal	Changes in levels of estrogens and progesterone
Metabolic	Increased water and sodium retention
Psychological	Stress, anxiety related to the pregnancy or other causes
Pharmacokinetics	Decrease in serum levels of AEDs due noncompliance, delusional effect or altered drug clearance
Physiological	Sleep deprivation, Physical strain

Effect of Epilepsy on Pregnancy

Infertility

It is generally considered that WWE have reduced fertility rate [1,10,11]. The proportion of women who get married and the age at marriage can influence fertility rate. The demographic, social, economic and medical factors that influence marriage in WWE need further examination [12]. It appears that women with epilepsy have increased tendency for polycystic ovarian disease (PCOD) [13]. Use of sodium valproate (VPA) had been shown to correlate with presence of PCOD that reverses when VPA is substituted by another AED [14]. A recent consensus report has recommended that if a reproductive endocrine disorder is found in WWE, AED treatment should be reviewed to ensure that it is correct for the particular seizure type and that it is not contributing to the endocrine problem. The possible benefits of a change in treatment must be balanced against seizure control and the cumulative side effect of alternative agents [15].

Complications of pregnancy

A recent prospective study of 643 pregnancies in WWE showed that the complications of pregnancy were comparable with those without epilepsy except for spontaneous abortions, anemia, ovarian cyst and fibroid uterus [16]. Nevertheless, several other studies did not show any excess risk of abortion when compared to others [17,18]. There are conflicting reports regarding the increased risk of non-proteinuric hypertension,[19]. pre eclampsia, eclampsia and abruptio placenta in WWE. Frequency of caesarean section may be increased for WWE although most of them can have normal vaginal delivery [20]. Uterine inertia, seizures and failure of progression of labor are usual causes of caesarian section [21]. (Table 2) A generalized seizure at term can cause transient fetal asphyxia as evidenced by cardiotocography. Fetal bradycardia, reduced variability and decelerations are seen for about 15 minutes after grand mal seizure [22]. Most WWE can expect an uneventful pregnancy and delivery.

Effect of Epilepsy and AED on fetus

Low birth weight, reduced length and head circumference have been observed the newborns [23]. Physiological impairments that were noticed in the

Table 2. Indications for cesarean sectin in WWE.

Elective cesarean section
Substantial neurologic or mental retardation
Reduced cooperation of the patient for labor
Very poor control of seizures
Daily complex partial seizures
Weekly tonic clonic seizures
Uterine inertia
Failure of induction of labor
Heavy sedation for patient
Emergency cesarean section
Generalized seizures during labor or near term
Fetal asphyxia
Other obstetric indications

newborns include low. Apgar score and failure to thrive. Babies born to mothers taking phenobarbitone may experience mild transient irritability due to the withdrawal effect of phenobarbitone. Rarely withdrawal seizures have been noticed in exposed neonates.

Malformations

The risk of malformation in the baby is one of the major concerns for WWE. Malformations refer to major abnormalities that require surgical intervention within the first year of life or are likely to result in significant impairment and disability e.g. Neural tube defects (NTD), congenital heart disease or cleft palate. Anomalies are minor deviations from normal development that may not cause significant impairment or disability e.g. Hypertelorism, acral hypoplasia of nails. In 1964, Janz first drew attention to the possible teratogenic effects of AEDs. Since then several fetal syndromes such as fetal hydantoin syndrome, fetal ethosuximide syndrome and fetal phenobarbitone syndrome have been described. The commonly observed malformations may affect cardiovascular system, gastro intestinal system, skeletal and connective tissues, and central nervous system [24]. (Table 3) It had been observed that the malformations observed with different AEDs share much in common and are often indistinguishable. Hence they are often referred to as fetal AED syndromes.

A joint European prospective study of human teratogenesis associated with maternal epilepsy has recently shown that most of the commonly used AEDs carry a relative risk of malformations when used in mono or polytherapy [25]. Several groups of medical professionals have been examining this issue over many decades through registries of epilepsy and pregnancy

Table 3. Incidence of malformations among 3228 children born alive of mothers treated with anti epileptic drugs.

System	Malformations	N	%
CVS	TOF, ASD, VSD, PDA, Pulmonary Atresia, single ventricle	66	2.0
Craniofacial	Cleft lip, Cleft palate	59	1.8
Skeletal	Club foot, hip dislocation etc.	29	0.9
CNS	Neural tube defects	23	0.7
GIT	Esophageal Atresia, CHPS Omphalocele, Hernia (diaphram, inguinal, umbilical)	10	0.3
GUT	Renal agenesis, Hydronephrosis Hypospadias, Undescended testes	11	0.3
Others		45	1.4
Total		243	75.

ASD = Atrial Septal Defect
PDA = Patent Ductus Arteriosus
CHPS= Congenital Hypertrophic Pyloric Stenosis,
TOF = Tetrology of Fallot
VSD = Ventricular Septal Defect

in several countries. None of the commonly used AEDs are free from teratogenic effects. A community based study of 1398 AED exposed infants from Sweden (90% as monotherapy) had shown that odds ratio for neonatal diagnosis of malformation was 2.52 (95% CI 1.43-4.68) for those exposed to VPA in monotherapy compared with Carbamazepine (CBZ) in monotherapy [26]. The North American Registry of Pregnancy and AED usage had recently demonstrated that antenatal use of phenobarbitone (PB) increases the relative risk of major malformations to 4.2 compared to a background risk of 1.62% [27]. The same group has also shown that the relative risk of having an affected offspring for VPA-exposed women was 7.3 (95% CI: 4.4 to 12.2; $p < 0.001$). They had identified sixteen affected cases among 149 VPA-exposed women (proportion: 10.7%; 95% CI: 6.3 to 16.9%). The prevalence in the internal comparison group was 2.9% (95% CI: 2.0 to 4.1%; odds ratio: 4.0, 95% CI: 2.1 to 7.4; $p < 0.001$) and external comparison group was 1.62% [28].

In a recent meta analysis of 59 papers published from various pregnancy registries, a cohort of 65,533 pregnancies in WWE were compared with 1,817,024 in healthy women. The calculated incidence of births with congenital malformations in WWE [7.08%; 95% CIs 5.62, 8.54] was nearly three times higher than healthy women

[2.28%; CIs 1.46, 3.10]. Incidence was highest for AED polytherapy [16.78%; CIs 0.51, 33.05]. The AED with the highest CM incidence was valproate, which was 10.73% [CIs 8.16, 13.29] for valproate monotherapy [29].

Several new AEDs have come in to the market in the last decade. The scope of newer AEDs in the management of epilepsy and pregnancy needs careful evaluation. It is important to remember that currently we have only meager data on the safety of newer AEDs with regard to human pregnancy and great caution should be exercised while interpreting them. Oxcarbazepine (OXB) has several pharmacological properties favorable for pregnancy. According to a recent report on 55 pregnancies with OXB (35 monotherapy), one malformation (cardiac) was observed with combination of OXB and PB and none with monotherapy [30]. In a series of 309 infants (from six countries) exposed to OXB (248 as monotherapy) the malformation rates were 2.4% for monotherapy and 6.6% for the adjunctive therapy group. The relative risk of malformation for OXB monotherapy appeared to be comparable to that in community [31].

Clinical trials of lamotrigine (LTG) started in 1984 and by turn of the next decade several thousand patients had been prescribed this drug. It is a broad spectrum AED with clinical indications similar to VPA. The U.K. registry reported a higher malformation rate with VPA, 5.9% (4.3-8.2%; 95% CI), than with CBZ, 2.3% (1.4-3.7%), and LTG, 2.1% (1.0-4.0%). International Lamotrigine Registry had published their results recently [32]. Among 414 first trimester exposures to LTG monotherapy, 12 outcomes with major birth defects were reported (2.9%, CI 1.6-5.1%). The risk of malformations after first trimester exposure to LTG monotherapy was similar to that observed in general population. Nevertheless, the risk of major birth defects was much higher (12.5%, 95% CI 6.7-21.7%) when LTG was combined with VPA in the first trimester. These preliminary results indicate that LTG may have a less teratogenic potential than VPA. Nevertheless, several other factors also need to be taken in to consideration. It appears that LTG and TPM have lower efficacy against idiopathic generalized epilepsy, when compared with sodium valproate. In a series of 962 persons with idiopathic generalized epilepsy, one year remission was highest (52.1%) for of persons using VPA monotherapy and lower for those using TPM (34.6%) and LTG (16.7%) monotherapy [33]. Persons on LTG may experience increase in seizure frequency during pregnancy because LTG is eliminated much faster than during non-pregnant state [34]. The concentration of lamotrigine in breast milk is higher than that for other AEDs [35,36]. Breast fed infants may occasionally have blood levels in therapeutic range. Most of the recent studies indicate that the risk of NTD in the offspring seems to be much less with lamotrigine, when compared to sodium valproate but this needs further validation [37].

There is only limited information available regarding safety of Vigabatrin during pregnancy [38]. Fewer pregnancies have been prospectively identified among women receiving gabapentin, tiagabine, topiramate and levetiracetam. Efforts are being made to systematically collect such data through registries [39, 40]. If one of the newer AEDs is the most efficacious and best tolerated AED for a woman, the general principles for pregnancy care should be followed as for the established AEDs. Topiramate (TPM) passes freely across placenta and appears to a limited extent (60-80%) in breast milk. Breast fed infants had only negligible concentrations of TPM [41]. Preliminary data from phase IV studies indicate that levetiracetam has no unfavorable effects on the fetus [42,43].

Neuro-cognitive development and AED exposure in-utero

Most babies born to WWE are normal. Recent reports suggest that these babies may have an increased risk of developmental delay or specific learning disabilities in children with prenatal exposure to AEDs particularly sodium valproate [44-46].

Preconception management

Preconception evaluation is the most important phase in the management of epilepsy and pregnancy. WWE need to have a neurological review at this stage, in order to ascertain the diagnosis and the need for continued treatment with AEDs. Most studies have shown that the risk of malformations in fetus is likely to be low with monotherapy, use of relatively lower dose of AEDs, spacing of daily dose in to multiple dosages and preconception use of folic acid. The controlled / extended release formulations of AEDs are likely to maintain a steady blood levels without much fluctuations. There is considerable variation in the risk of malformations with different AEDs even when used as monotherapy. Different AEDs carry different therapeutic efficacy against different seizure types. Physicians need to discuss these aspects with WWE and their partners, and explain the rational of selection

of AEDs. It may be possible to withdraw AED if the patient had remained seizure free for more than one or two years. The general guidelines for AED withdrawal as for patients in remission are followed in WWE also. Persons with Juvenile Myoclonic Epilepsy may have to continue AEDs, even when they had been seizure free for quite some time and the EEG was normal. In the case of high-risk pregnancies (with family history of NTD or previous pregnancies with birth defects) the option of an alternate AED need to be discussed with the patients although the second AED may also carry the potential risk. There is much debate regarding choice of AED for women with Juvenile Myoclonic Epilepsy who are contemplating pregnancy. The risk and benefits of VPA versus other AEDs such as LVT, LTG, TPM or PB need to be discussed with them so that the patients would be able to make an informed choice. High dosage VPA and combination of VPA and LTG may be avoided if possible in preconception period and early pregnancy since it carries higher risk of fetal malformations. A universal recommendation for antenatal care includes prescription of 0.4 mg of folic acid daily. We recommend folic acid 5 mg daily to all women who can potentially be pregnant.

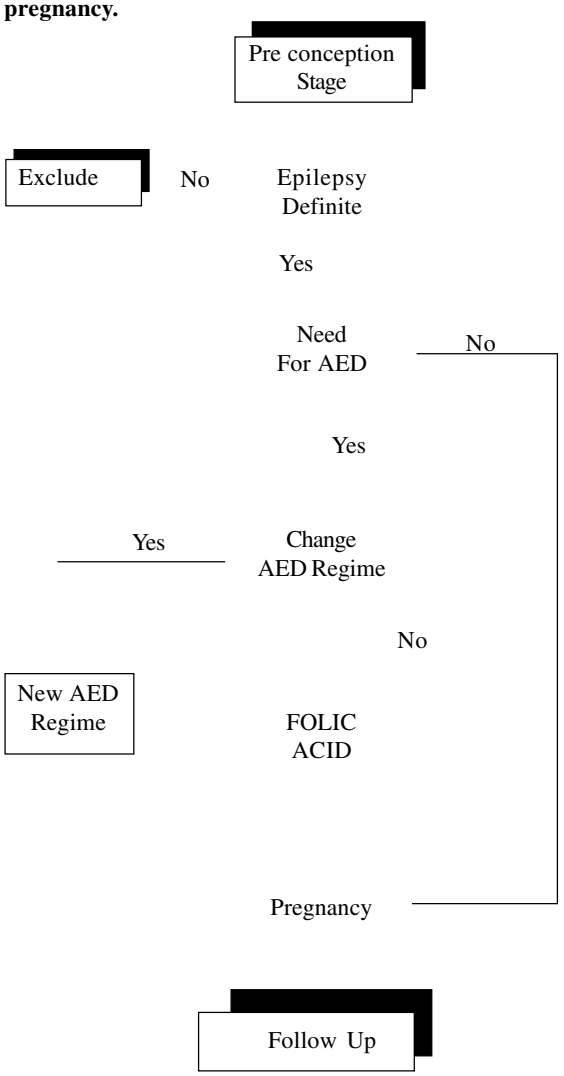
Scientific opinions differ with regard to the role of periodic monitoring of blood levels of AEDs during pregnancy. It is important to estimate the free drug levels if the patient experiences unexpected increase in seizures.

The general protocol for preconception management of WWE that is followed in the Kerala Registry of Epilepsy and Pregnancy (KREP) [47] is given in figure 1.

Management of epilepsy during pregnancy

Seizures tend to improve or remain unchanged in nearly two thirds of WWE [48] . The risk of seizures is higher in the first trimester of pregnancy and around delivery time. It may be possible to shift patients from polytherapy to monotherapy. It is preferable to keep the total daily dose of VPA below 800 mg as higher doses have been implicated with increased risk of NTD. It is important to ensure good compliance with AEDs through out pregnancy in order to avoid relapse of seizures. The dosage of AEDs may have to be increased in some patients in the third trimester especially if the blood levels (preferably free drug levels) are low. The risk of seizure relapse around the time of delivery is three times more than during the rest of the pregnancy. The increased risk of seizure relapse is probably related to drug default, dehydration, prolonged fasting and effect of co medications, have been implicated for such relapse.

Figure 1. Algorithm for management of epilepsy and pregnancy.



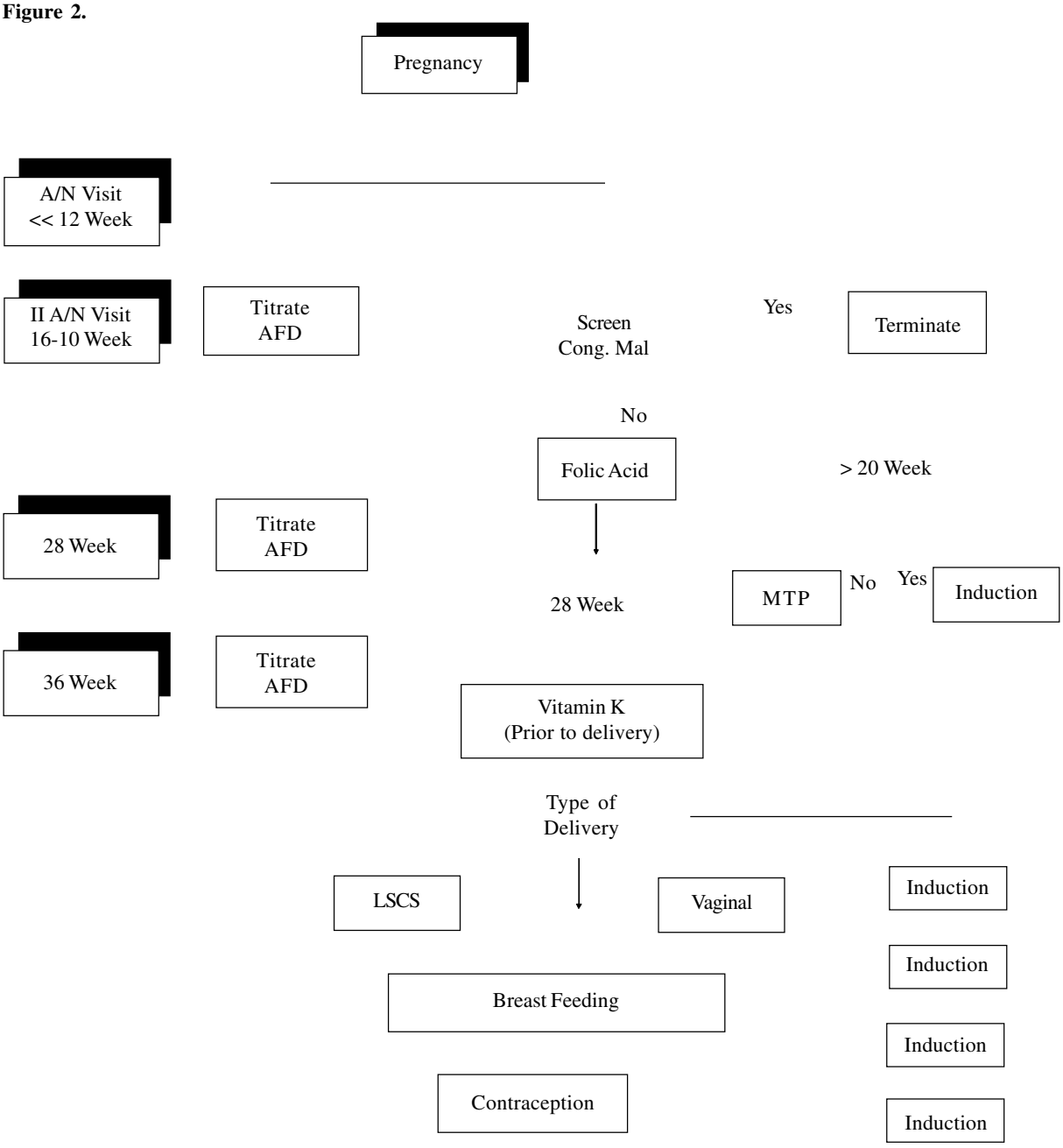
Status epilepticus can occur rarely during pregnancy essentially, when there is a drug default or a brain lesion. General guidelines for managing SE can be followed in such instances. The fetal outcome had been poor when it took a long time to control seizures [8]. The general schedule of antenatal check up should be followed in all WWE.

Monitoring for fetal malformations

Monitoring for fetal malformations should be carried out towards the end of first trimester. The first line screening procedure would be estimation of serum alpha

feto protein (AFP), which tends to be elevated in cases of open NTD. Serum levels of AFP increase gradually during the first trimester and tend to decline after the fourth month of pregnancy. Hence the levels should be correlated with the period of pregnancy preferably with conceptual age, calculated with the aid of ultrasonography. A recent trend is to express the AFP level as multiples of median for that period of pregnancy. This would make inter laboratory comparisons easier. AFP could be elevated for other reasons such as twin pregnancy, placental hemorrhage, etc. If the AFP levels are abnormally elevated the trend need to be ascertained by repeating the test after one or two weeks. The result also needs to be correlated with a detailed ultrasonography targeting fetal organogenesis. The management protocol that is followed in the KREP, [47] is given in figure 2.

Figure 2.



Ultrasonography has become an integral part of antenatal check up recently. Early detection of malformations such as spina bifida and meningomyelocele require careful ultrasonography. Amniocentesis and cord blood analysis may have to be resorted to in selected cases, where fetal karyotyping also may be required.

Counseling the family when an abnormality had been detected.

It is very important to counsel the patient and the family before the screening procedures as well as after the procedure. The family would require sensitive and detailed counseling if a serious malformation had been detected. The sensitivity and specificity of the findings are also explained to the family. Care should be taken to explain in simple terms the type of malformation that is identified and its possible impact on the fetal survival and quality of life. The various options available to the family such as termination of pregnancy, continuation of pregnancy and the scope of fetal surgery can be explained to the couple.

AEDs that induce hepatic C450 enzyme system appear to be associated with vitamin K deficiency in the newborn. Their use can result in hemorrhagic disease of the newborn leading to intraparenchymal and intracerebral hemorrhage. Administration of vitamin K1 to the mother can prevent hemorrhagic disease of the newborn [49]. It is generally recommended that pregnant women with epilepsy on enzyme inducing AEDs should be prescribed vitamin K1 10 mg/day during the last month of pregnancy. These neonates also should receive the customary dose of Injection Vitamin K 1 mg on the day of delivery. The obstetrician should plan the type of delivery based on the obstetrical indications. Nearly a third of our patients required cesarean section [16].

Postpartum management

The AEDs need to be followed using the same third trimester dosage in the first three months of postpartum period. Some patients would experience exacerbation of seizures during this period. It is helpful to arrange with the family members to share some aspects of caring for the newborn to avoid undue physical and emotional stress. The dosage of lamotrigine if it had been increased during pregnancy may have to be brought back to prepregnancy levels in order to avoid toxic levels in the mother and newborn.

Breast Feeding

Most of the AEDs tend to cross into breast milk in inverse relation to their protein binding. (see table 4) Newer AEDs tend to pass into breast milk in greater concentration than older drugs [50,51]. The benefits of breast-feeding probably far outweigh the potential risk to the infant. Nevertheless, infants need to be carefully monitored for any untoward effects attributable to AED exposure through breast milk. Monitoring of infant serum drug concentrations is advisable but not compulsory [52]. The general recommendation is to continue breast-feeding but the feeds may be given before the woman takes her AED doses.

Table 4. Anti epileptic drugs in breast milk as a proportion of blood levels.

Drug	Proportion appearing in breast milk
Valproate	<10%
Phenytoin	20
Carbamazepine	40%
Phenobarbitone	50%
Primidone	80%
Lamotrigine	61%
Topiramate	86%
Oxcarbazepine	80%
Zonisamide	41 - 57

Spacing and contraception

The family needs to be counseled about the need for proper spacing of further childbirth. Oral contraceptives, especially low estrogen preparations and progesterone implants may have reduced efficacy when used along with enzyme inducing AEDs (PHT, CBZ, OXB and PB) [53].

Topiramate may reduce the ethinyl estradiol level by a different mechanism [53]. In presence of such AEDs, it may be necessary to use oral pills with more than 50 micrograms of estrogen. Non-enzyme inducing AEDs such as VPA, LTG, GBT may not interfere with oral contraceptive pills [53]. Medroxyprogesterone depot injections taken once in three months or intrauterine devices can be used as alternate methods of contraception.

Conclusion

Women with epilepsy have several special problems related to pregnancy that need careful attention from the attending neurologists and obstetricians. It is comforting to know that majority of WWE can have safe pregnancy and childbirth. Fetal malformations attributable to exposure to AEDs occur in a small proportion of instances only and appropriate preconception management can probably reduce this risk

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