Epilepsy and pregnancy

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Pregnancy poses special problems to women with epilepsy. Seizures may aggravate in up to a third of such women, while others may experience no change or even an improvement. Teratogenic potential of anti-epileptic drugs (AEDs) remains the major concern for women with epilepsy, although close to ninety per cent of babies born to mothers taking AEDs are healthy. All commonly used AEDs have been implicated with fetal malformations. Several factors, such as concomitant use of two or more AEDs, very high daily dose, lack of folate administration and positive family history, have been identified as risk factors for fetal malformations. Several measures can be taken in the preconception period and pregnancy to reduce the risk of malformations and other complications of pregnancy and epilepsy. Access to a well-informed and proactive counselor is very helpful to the patients and their families in handling the diverse issues related to epilepsy and pregnancy. Women with epilepsy need an integrated care, from neurologist, gynaecologist and other specialists.

IT is estimated that there are about 2.5 million women with epilepsy (WWE) in India; some two-thirds of them are in the childbearing age group. Epilepsy poses greater challenge to woman at every major phase in her life, early adolescence, reproductive age group and menopause. There has been considerable progress in epilepsy care in the recent past. Several new anti-epileptic drugs (AEDs), with more favourable efficacy and adverse effect profile, have been released. Surgical therapy of epilepsy had matured into a distinct, safe and effective procedure of choice in selected cases of medically intractable epilepsy. The goal of treatment now focuses on improved quality of life rather than mere control of seizures. WWE are subject to considerable social discrimination and prejudice. In many parts of the world, there is undue apprehension about marrying WWE and strong prejudice against employing them. This discriminative social milieu is probably giving way to one of openness and acceptance. Recently the Government of India has amended the discriminative clause against epilepsy from the marriage act. A recent study from Kerala state has shown that 59% of women of childbearing age group attending the epilepsy clinic were married. This is only slightly lower than that for the women of similar age group (65%) in Kerala state[1]. Similar observations have been made from elsewhere also[2]. Neurologists and gynaecologists are increasingly faced with WWE during pregnancy, which is generally considered to be a high-risk situation. Two recent studies have shown that specialists caring for WWE are not optimally informed about the issues[3,4]. Another recent study in USA showed that services for WWE during pregnancy is sub-optimal in many respects[5]. There are many important aspects to managing pregnancy in WWE. Pregnancy influences the natural history of epilepsy and pharmacodynamics and kinetics of AEDs in a diverse manner. Further, AEDs may have adverse effects on the outcome of pregnancy.

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Effect of pregnancy on epilepsy

Epileptic syndromes during pregnancy

Seizures can occur during pregnancy or immediate postpartum period due to several causes. Seizures due to eclampsia, central nervous system infections, cerebral venous sinus thrombosis, and other acute medical conditions are grouped under special syndromes in the classification of epileptic syndromes according to the International League Against Epilepsy[6]. Recurrent seizures without any provoking factor only come under the category of epilepsies. In most such instances, seizures would have started before pregnancy. Rarely some women 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 one to two per cent of WWE may experience status epilepticus during pregnancy, which is associated with high morbidity and mortality.

Effect of pregnancy on epilepsy

There is wide variation in the reported statistics on seizure frequency during pregnancy. Several methodologi-

cal issues make it difficult to make comparisons between studies. In many instances, authors have not distinguished between partial seizures and generalized seizures. It is possible that subtle partial seizures were not listed in some of the retrospective studies. In some studies, authors have referred to seizure patterns through the entire period of pregnancy whereas others have distinguished between various trimesters of pregnancy. Some reporters have given the seizure count while others have only mentioned whether seizures had increased or decreased during pregnancy. There can be variations in the definition of improvement or worsening. In general, nearly a third of WWE experience increase in seizure frequency while another third experience a decrease in seizure frequency. Others may have no change in seizure frequency. Seizure frequency may vary between pregnancies in the same woman also.

In a large meta analysis, Schmidt had reviewed 27 publications[7] between 1884 and 1980. There were 2165 pregnancies, of which 522 (24.1%) had increase in seizure frequency, while 492 (22.7%) had decrease, and 1151 (53.2%) had no change in seizure frequency. There were 12 (0.53%) instances of status epilepticus. In a preliminary analysis of data from 122 patients in the Kerala Registry of Epilepsy and Pregnancy (KREP), it was observed that mean seizure frequency during the 12 months prior to current pregnancy was 2.02 ± 10.4. (Fifty women were seizure-free.) Seizure counts for each month of pregnancy and three postpartum months were compared with the pre-pregnancy seizure frequency. About 1% of these patients had status epilepticus. The mean seizure frequency for the cohort remained lower than pre-pregnancy levels throughout pregnancy and puerperium. Two patients had status epilepticus. Seizure frequency tends to improve during pregnancy and puerperium in most women with epilepsy[8].

The trimester-wise analysis indicates that seizure frequency is least during the third trimester and postpartum period[9–11]. Our data also indicate that seizure control during late pregnancy is better than in early pregnancy. However, in our study, seizure frequency during the 72 h around delivery (3) was more than that of the baseline (2.02) and many fold more than that of the previous and ensuing month (0.8 and 0.2 respectively). The increased risk of seizure relapse during the peripartum period stands out when compared to the more favourable seizure frequency during the III trimester and postpartum period, which may be attributed to failure to take medicines, physical exhaustion, relative hypoglycemia or other metabolic derangements.

Diverse patterns of seizure relapse can occur during pregnancy. They may have a stable pattern with seizure frequency remaining more, less or unchanged throughout the entire period of pregnancy, when compared to pre-pregnancy period. Others may have an unstable pattern, wherein the seizure frequency may vary widely and often unpredictably during different months of pregnancy. In a recent study through the KREP, we had observed that nearly 61% patients had a stable pattern and 39% women had an unstable pattern[12]. Knight *et al.* had described a bimodal pattern of seizure aggravation during the early pregnancy and in the peripartum period[38]. When seizures recur during pregnancy in women who were previously under good control, most often it takes place during the first and second trimesters[13]. An increase in seizure frequency is more likely in women with a high pre-gravid seizure frequency or multiple seizure types. The risk of seizures is greatest in the delivery period with tonic clonic seizures complicating labour in 1–2% cases and a further 1–2% in the following 24 hours[14].

Several mechanisms have been put forward to explain the change in seizure frequency during pregnancy. Estrogens are found to increase seizures in animal models and human beings. Progesterone on the other hand, lessens spontaneous and induced epileptiform discharges[15,16]. It was recently shown that pregnancy is associated with a significant down regulation of NMDA and non-NMDA receptor binding in rats, a finding that suggests that pregnancy affords some protection against seizures induced by an activation of NMDA receptors in the brain[17]. Several other important factors, such as noncompliance and decrease in blood levels of free-form of AEDs, influence it (see Table 1). While discussing the causes of aggravation of seizures, care should be taken to exclude psychogenic seizures, which may appear for the first time or persist during pregnancy[18,19].

The plasma concentration of AEDs tend to decrease during pregnancy as a result of a 50% increase in plasma volume, decrease in protein binding, decreased absorption, increased clearance and tendency for decreasing patient compliance.

SE is rare (less than 1%) during pregnancy. Most of SE occurs during third trimester[20]. In the Kerala Registry of Epilepsy and Pregnancy (KREP) cohort, the incidence was 0.8%. Symptomatic epilepsy associated with structural abnormalities of brain is more likely to develop status epilepticus during pregnancy. The overall prognosis is poor for SE.

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, dilution effect or altered drug clearance
Physiological	Sleep deprivation, physical strain

Effect of epilepsy on pregnancy

Fertility in epilepsy

Women with epilepsy are reported to have lower fertility rates[21–23]. Marriage rates are lower among women with epilepsy[24–26]. However, even within marriage, fertility can be lower for WWE as shown in a recent epidemiological study in UK where the standardized fertility rate for WWE who are under treatment and in the age group of 25–39 was lower than that in the community[27]. In contrast, a community-based study in Iceland indicated that WWE have no reduction in fertility rates[28]. Pregnancy is more likely to occur in women with fewer or no seizures[29]. It is possible that epilepsy or AEDs may reduce fertility. A recent study has shown that barbiturates inhibit synthesis of progesterone in cultured leydig cells[30]. Anti-epileptic drugs, particularly, sodium valproate (VPA) may induce polycystic ovarian syndrome characterized by obesity, menstrual irregularities and anovulatory cycles, and virulizing effect. Issues related to fertility need to be discussed with the patient.

Polycystic ovarian syndrome (PCOS) consists of obesity, anovulatory cycles, irregular menstrual periods and infertility. It is due to polycystic ovarian changes (PCO) associated with elevated levels of androgens, or leutinizing hormone. Estimates of prevalence of PCO vary from 22 to 33% and PCOS varies from 5 to 26% among adult women in UK[31,32]. Isojarvi *et al.*[33] had suggested that about 64% of VPA-treated women might have either PCO or PCOS[34]. These effects were more common among women beginning VPA therapy before the age of 20 years. These changes are reversible on stopping VPA[35]. In contrast to the above observations, certain studies failed to observe any association between VPA and PCOS[36,37].

Complications of pregnancy

Most pregnancies are uneventful in WWE and most babies delivered are healthy. WWE may experience minor complications of pregnancy such as hyperemesis, more frequently. One of the major concerns for a WWE is the risk of abortion, especially in relation to active seizures. Most of the recent studies have shown that the risk of abortions among WWE is not more than that in the community[38–40]. The incidence of pre-eclampsia, eclampsia and abruptio placenta may be more in WWE. Nearly a third of pregnancies among WWE end in Caesarian section although most of them can have normal vaginal delivery[41] (see Table 2). A generalized seizure at term can cause transient fetal asphyxia. Data from the KREP indicate that WWE have no increased risk of complications of pregnancy or Cesarean section.

Perinatal mortality is increased by 1.2–2 times[42]. Maternal complex partial seizures can cause fetal bradycardia[43]. There are anecdotal reports of miscarriages due to complex partial seizures.

Effect of epilepsy and AEDs on fetus

The effects of epilepsy and AEDs on the baby can be classified into (a) anthropometric changes, (b) minor anomalies, (c) major malformations, (d) physiological derangements and (e) late effects. The risk of malformation in the baby is one of the major concerns in epilepsy. Deviations from normal development can be classified into major malformations and minor anomalies. Malformations refer to major abnormalities that might require surgical intervention within the first year of life or those that are likely to result in significant impairment and disability, e.g. neural tube defects, 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.

Anthropometrical effects

Minor variations in anthropometric features have been observed in infants of mothers with epilepsy (IME). Low birth weight, reduced length and head circumference have been observed in certain studies[44]. Several authors in the past have documented an association between maternal epilepsy and *in utero* exposure to AEDs with intrauterine growth retardation[45–48]. Such an association was not validated in studies from elsewhere[49–54]. This discrepancy can partly be explained by the difference in study design (prospective vs retrospective) techniques of data analysis (absolute measurements with or without correction for gestational age, etc.). Some authors have described the data in relation to control values for the country or international standards. A dose-dependent

Table 2. Indications for Caesarian section in WWE

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

effect was found for phenobarbitone (PB) and primidone (PRM) in terms of small head circumference and low birth weight[55]. A concentration-dependent effect for PB in terms of small head circumference was also demonstrated. Ethnic, genetic and environmental factors also need to be taken into consideration, as there was significant variation with relation to the country of study. Another analysis from Stockholm, Sweden indicates that risk factors for small babies are polytherapy or carbamazepine (CBZ) monotherapy[56].

Minor anomalies

Several minor anomalies have been reported in IME. These include hyperptelorism; low-set ears, digital hypoplasia, etc. A recent study from Mexico failed to demonstrate any differences in the facial measurements among babies exposed to different AEDs used in monotherapy[57]. Other anomalies that were recently reported include glued ears, laxity of joints, and myopia[58,59]. According to a study that compared vision and fundus findings in 40 children born to mothers taking AEDs with healthy controls, there was no impairment of visual functions or other ophthalmologic abnormalities among IME[60].

The precise pathogenesis of these anomalies remains unknown. The similarity in facial appearance of children exposed *in utero* to warfarin and CBZ and the potential for both drugs to induce vitamin K deficiency and bleeding tendency in the newborn have raised the possibility that abnormal facial development may be related to vitamin K deficiency. Minor anomalies that are described as part of fetal hydantoin syndrome were also hypothesized to be associated with maternal epilepsy and not necessarily with the anticonvulsants[61,62].

Malformations

In 1964, Janz first drew attention to the possible teratogenic effects of AEDs[63]. The first systematic study in English language was by Meadow[64]. Since then, several fetal syndromes such as fetal hydantoin syndrome, fetal ethosuximide syndrome and fetal phenobarbitone syndrome have been described. Subsequently the teratogenic potential of CBZ and VPA was also documented.

It is fascinating to trace the evolution of knowledge in this field over the decades. In studies before 1930s, even before the advent of modern AEDs including PB, it was observed that children born to mothers with epilepsy have increased incidence of minor and major congenital abnormalities. This was regarded as the expression of deficient structural differentiation and as indicators of disturbances in brain maturation correlated with epilepsy itself[65]. Since the 1960s the emphasis had shifted to the teratogenic effects as the mechanism of congenital abnormalities. In the 1980s several biochemical mechanisms and genetic factors contributing to teratogenesis were recognized. Recently other demographic factors have also been implicated in teratogenesis.

A meta-analysis of over two thousand pregnancies among WWE has shown that 5.1% cases have had major malformations. The frequency of malformation was much higher (up to 10%) in more recent prospective studies. The commonly observed malformations may affect cardiovascular system, gastrointestinal system, skeletal and connective tissues, and central nervous system (see Table 3). It had been observed that the malformations associated with different AEDs share much in common and are often indistinguishable. Hence they are referred to as fetal AED syndromes.

Several groups of medical professionals have been examining this issue over many decades through registries of epilepsy and pregnancy in several countries. None of the commonly used AEDs are free from teratogenic effects even though the risk may be small. 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[66] (see Table 4).

Dean *et al.*[67] have developed an evaluation protocol with six aspects that may be useful in recording the AED effect and AED syndromes. These authors have suggested certain criteria for diagnosing fetal anticonvulsant syndromes[68].

Table 3. Incidence of malformations among 3228 children born alive of mothers treated with anti-epileptic drugs (25 cohort)

System	Malformations	N	%
CVS	TOF, ASD, VSD, PDA, Pulm. 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	Esoph. Atresia, CHPS, Omphalocele, Hernia (diaphragm, inguinal, umbilical)	10	0.3
GUT	Renal agenesis, Hydronephrosis, Hypospadias, Undescended testes	11	0.3
Others		45	1.4
Total		243	7.5

Table 4. Relative risk (RR) for congenital malformations with exposure to various AEDs in mono or polytherapy

AED	Pregnancies N (%)	RR
Non-epileptic controls	12/58 (8)	1.0
CBZ	4/14 (29)	4.9
PB	1/6 (17)	2.4
PHT	5/33 (15)	2.2
PRM	3/39 (8)	1.0
VPA	6/21 (29)	4.9
PHT +PB	2/15 (13)	1.8
PRM +VPA	1/13 (8)	1.0
Others	8/51 (16)	2.1

CBZ, Carbamazepine; PB, Phenobarbitone; PHT, Phenytoin; PRM, Primidone; VPA, Valproic acid.

Several large studies have shown an increased risk of major malformations when the baby was exposed to AEDs *in utero*[69–73]. The occurrence of specific malformations may depend on timing of exposure during embryogenesis. Neural tube defects occur before closure of the neural tube between 21 and 28 days, cleft lip occurs before 35 days and cleft palate before 70 days whereas congenital heart defects occur before 42 days[74].

According to Samren's study, phenytoin (PHT) and PB were relatively safer than CBZ and VPA. Use of caffeine along with PB increased the risk of malformations. Polytherapy, particularly involving clonazepam, was associated with increased risk of malformations.

An Italian group has classified various malformations into five categories[75]. According to this Italian study involving 517 pregnancies, the overall rate of malformations was 9.7%, of these 5.3% were structurally severe, 2.2% were mild, 0.4% were chromosome-genetic and 1.8% were deformities. No malformation was detected in the 25 untreated patients.

In a study of 161 patients undergoing VPA therapy (mono or polytherapy) about 30% were detected to have major malformations involving heart, palate, or spinal cord[76]. Three cases of lung hypoplasia have been reported in babies exposed to VPA *in utero*[77]. The overall incidence of malformations in pregnancies among WWE was 9% in a large study, involving 983 pregnancies from Italy, Canada and Japan[78]. The odds ratio for malformations increased from monotherapy to polytherapy (see Table 5). Drug scoring system of Kaneko helps to convert the individual dosage to comparable values[79].

Mechanism of AED-induced teratogenicity

Several mechanisms have been proposed to explain the teratogenic effects of AEDs.

Free radical toxicity. Some of the AEDs (phenytoin) form intermediate oxide metabolites, which are known to be embryotoxic. Free active oxide radicals have been shown to bind to proteins and nucleic acids and may interfere with DNA and RNA synthesis. Critical amounts of free radicals may increase the risk of perinatal death, intrauterine growth retardation and malformations[80].

Scavenging enzyme deficiency. Normally the free radical scavenging enzymes conjugate the free radicals and prevent embryotoxicity. It has been proposed that fetuses with low levels of free radical scavenging enzymes and low activity of epoxide hydrolase are at increased risk of developing malformations associated with phenytoin. Polytherapy may lead to excessive amounts of unstable epoxides such as arene oxides and inhibit epoxide metabolism especially in fetuses with a genetic defect in epoxide hydrolase activity[81].

Folate deficiency. Folate deficiency is another important mechanism of teratogenesis, especially for neural tube defects (NTD). Comprehensive reviews of folic acid and NTD had been published recently[82,83]. Certain geographic areas and ethnic groups carry increased risk of NTD. Hispanics in the Texas state of USA show increased prevalence of 13–19 per 10,000 population[84]. Recent studies raise the possibility of impaired absorption of folate from the gut as one of the mechanisms that lead to folate deficiency in pregnant women[85,86]. Studies in murine models using knockout and knockdown folate receptors indicate that there are folate receptors that facilitate transplacental transport of folate. Folate receptors are critical for the development of neural tube and neural crest. Depending on the time of relative folate deficiency, the clinical manifestations could differ. Early deficiency may lead to NTD and late deficiency to small for date babies[87]. Several epidemiological studies indicate that folic acid deficiency increases the risk of neural tube defects. Dietary fortification of cereals with folate was associated with a decline in the incidence of NTD in Scotland and Ireland by 5–12% during the last two

Table 5. AED combination profiles and incidence of malformatons

AED	AED2	MALF	TOT	OR	%
0		3	98	3,1	
PHT		12	132	3,2	9,1
PB		4	79	1,7	5,1
PRM		5	35	5,3	14,3
CBZ		9	158	1,9	5,7
VPA		9	81	4,0	11,1
CBZ	VPA	3	14	8,6	21,4
PHT	OTH	2	11	7,0	18,2

CBZ, Carbamazepine; PB, Phenobarbitone; PHT, Phenytoin; PRM, Primidone; VPA, Valproic acid; OTH, Other anti epileptic drugs; AED, Monotherapy; AED2, Polytherapy with two drugs; MALF, number of cases of malformation; TOT, Total number of babies; OR, Odd's Ratio.

decades[88]. Administration of folic acid in the periconception period reduced this risk among the high-risk group in Texas state[89]. However, there are some questions about the efficacy of folic acid in reducing the risk of NTD[90,91]. Folic acid may have weak epileptogenic property[92] and may aggravate seizures in rare cases[93].

Up to 90% reduction in folate serum levels was reported in patients treated with PHT, CBZ and barbiturates. Valproic acid did not reduce folate levels directly, but interferes with its metabolism[94,95]. Two randomized controlled trials published in early 1990s have confirmed that periconceptional folate supplementation reduces the risk of NTD[96,97]. Presently however, there is no data to document the efficacy of folate in women with epilepsy, but potential benefits far outweigh the risk associated with high dosage folate. The Medical Research Council study reported a 70% reduction of NTD recurrence among women who were supplemented with folic acid 4 mg before conception and during gestation. The CDC recommendation is to supplement 0.4 mg folate daily[98]. Several other factors are also suspected to be associated with increased risk of NTD. Prepregnancy obesity and high maternal homocysteine levels (which in turn may be related to folate deficiency) carries a two-fold increased risk. Epidemiologic data indicate that low socioeconomic status and residence in such neighbourhood increases the risk of NTD[99].

Genetic factors. Genetic factors had been attributed to cause malformations in infants, particularly when exposed to AEDs. Variable teratogenicity among inbred strains of laboratory mice suggests that genetic factors influence susceptibility. Altered expression of specific *Hox* genes may account for the homeotic transformations and other malformations found in VPA-treated fetuses. But multifactorial mechanisms that alter gene expression may be operational in AED-induced NTD[100]. This study, carried out in mice, has demonstrated that embryos from these two strains behaved differently, not only in response to VPA exposure, but also under control conditions, which may explain the multifactorial nature of NTD.

Maternal epilepsy. Minor anomalies observed in IME have been postulated to be related to the maternal epilepsy in certain studies[101,102].

Physiological changes

Physiological impairments that were noticed in the newborns include low apgar score and failure to thrive. Babies born to mothers taking PB may experience mild irritability due to the withdrawal effect of PB that disappears in a few days time. Rarely have babies been noticed to have PB withdrawal seizures.

Hemorrhagic disease of newborn. Maternal use of anticonvulsants may interfere with the metabolism of Vitamin K and synthesis of coagulation factors in the fetus. The association between maternal anticonvulsant therapy and neonatal hemorrhage was first reported in 1958 from France. These hemorrhages occur typically during the first 24 h after birth, in contrast to the classic neonatal bleeding that occurs on day two or three after delivery. It may involve skin, brain or pleural cavity and can be severe. Enzyme-inducing AEDs like PB, PRM, PHT and CBZ have been implicated in this.

Vitamin K is important in the formation of clotting factors II, VII, IX and X. When prothrombin is formed in the liver, it contains 10 glutamic acid residues that need to be carboxylated to form fully functional prothrombin. In vitamin K deficiency, the prothrombin either remains uncarboxylated or it is only partially carboxylated and is known as PIVKA II. The amount of PIVKA II in the blood is a measure of vitamin K deficiency.

Prothrombin and PIVKA II levels in the cord blood had been found to be abnormal when fetus was exposed to different AEDs particularly CBZ[103]. In a case control study Cornelissen *et al.*[104] have shown that, when pregnant women taking AED were given vitamin K from 36 weeks of pregnancy onwards, the cord blood samples were negative for PIVKAII. In contrast, those who were not receiving vitamin K, tested positive. Their observation indicates that vitamin K supplementation during the last month of pregnancy reduces the risk of hemorrhagic disease of the new born, when the mother is taking AEDs.

Late effects of AED on babies

Relatively little attention had been focused on the developmental aspects of infants of mothers with epilepsy. Results of some of the published studies vary in their observations. In a prospective evaluation of 47 children exposed *in utero* to CBZ, mild mental sub-normality was observed when examined between 6 months to 6 years[105]. Another prospective study of IME failed to reveal any impairment of development[106].

Newer AEDs and fetal outcome. Several AEDs have come into the market in the last decade. The scope of newer AEDs in the management of epilepsy and pregnancy needs careful evaluation. Except for topiramate (TPM), which is associated with limb agenesis, none of the newer AEDs have been shown to be teratogenic in animals (see Table 5). Lamotrigine Pregnancy Registry is maintained by Wellcome group and includes all pregnancies that have voluntarily and prospectively reported to the registry[107,108]. Between 1992 and 1998, there were 6 cases of birth defects (5.6%) associated with first trimester exposure to lamotrigine (LTG) therapy. There was no consistent pattern of malformations among de-

fects reported. In the prospective reports of all trimester exposure combined there were no birth defects in 37 outcomes. The advisory committee of this registry concluded that the number of exposed pregnancies outcome represent a sample of insufficient size for reaching definitive conclusions. However, congenital anomalies have been reported with vigabatrin in combination with CBZ[109]. Fewer pregnancies have been prospectively identified among women receiving GBT, tiagabine (TBG) and TPM. Efforts are being made to systematically collect such data through registries[110]. 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. In general, newer AEDs have better side effect profile. They possess many distinct pharmacodynamic and pharmacokinetic properties that make them potentially safer during pregnancy.

Management of epilepsy in preconception period

Management of epilepsy and pregnancy demands sound knowledge on the complex interaction between epilepsy, pregnancy and the fetus. Efficient care during pregnancy is best achieved through an integrated programme in which, experts from neurology, gynecology, imaging specialty, and pediatrics work together. The services of a clinical geneticist and social worker are also desirable (see Figures 1 and 2).

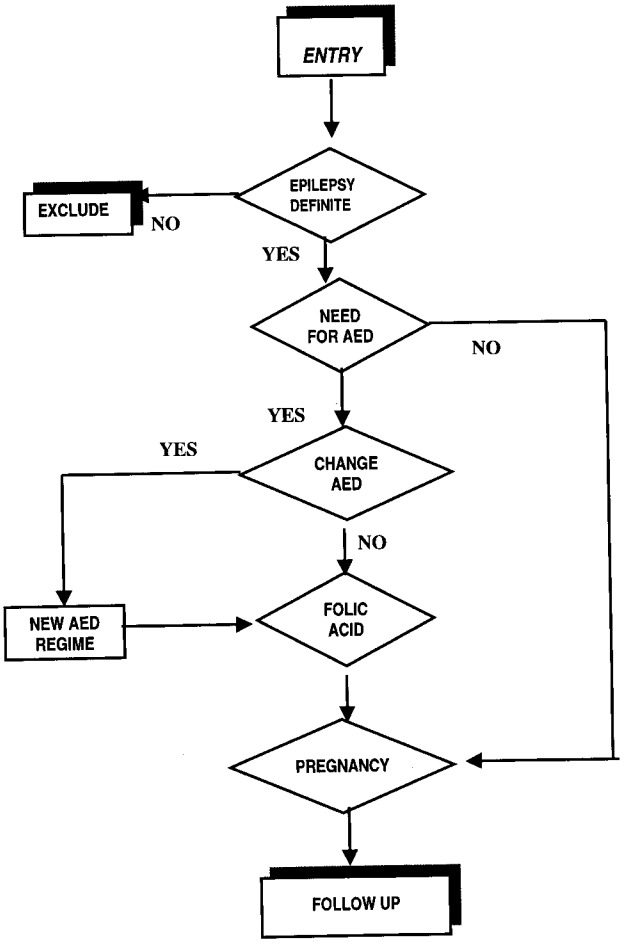

Figure 1. Algorithm for preconception management of epilepsy.

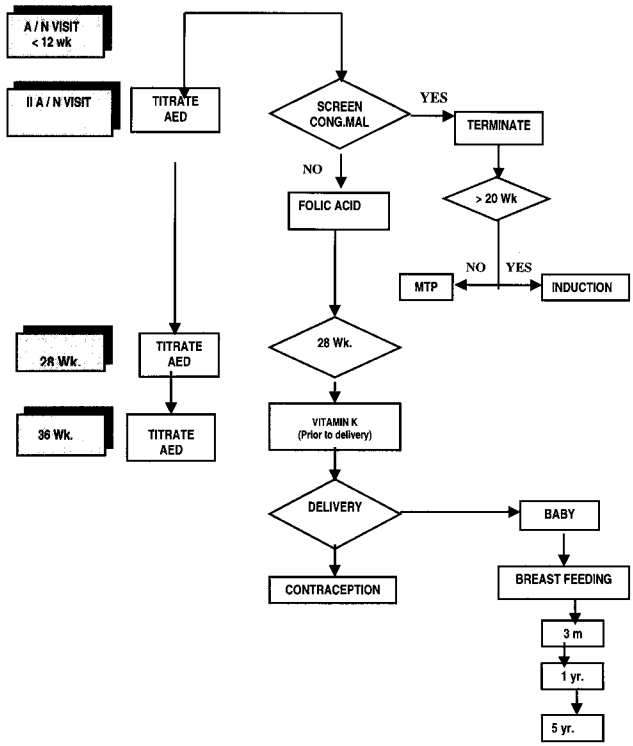

Figure 2. Algorithm for management of epilepsy and pregnancy.

Counseling

There are many apprehensions in the mind of the patient and her family about epilepsy and pregnancy. The physician or the counselor needs to maintain a sympathetic and positive attitude while discussing the various issues in the light of available scientific data. Recent trends have been to provide directive counseling that emphasizes these points[111]. The experience from Scotland indicate that proactive counseling improves the outcome of pregnancy in WWE in terms of reducing the AED load, reducing the birth defects and improving the control of seizures[112]. The common issues raised during these discussions are related to the safety of pregnancy in WWE, risk of aggravation of seizures during pregnancy, risk of fetal malformations or epilepsy in the infant, and the precautions that need to be adopted.

Preconception management of epilepsy is very important from a risk reduction viewpoint. The first step is to establish the diagnosis and decide on appropriate management. Some of the patients who are erroneously diagnosed with epilepsy can be taken off AEDs after

exclusion epilepsy. It is important to recognize that at least 10% of teenagers thought to have epilepsy actually have a non-epileptic disorder[113]. Common misdiagnoses include syncope, migraine. In several young women who are in remission, it is possible to discontinue AEDs after proper assessment. In the case of juvenile myoclonic epilepsy, it is often possible to switch to monotherapy or reduce the dosage. A detailed pedigree charting with reference to epilepsy, early mortality and congenital malformations is very helpful while counseling the patient regarding these risks in the offspring.

The general principle is to use the least effective dose of an AED appropriate to the epileptic syndrome, preferably in monotherapy (see Table 6). The broad principles followed in the KREP are discussed below. Selection of AED is always individualized on the basis of several factors including EEG findings, specific epileptic syndrome and the patient's experience with that drug in terms of seizure control and complications of pregnancy including teratogenicity. Combination of CBZ and VPA and VPA monotherapy with doses higher than 1000 mg are to be avoided in view of its higher risk of teratogenicity. The total daily dose of CBZ and VPA need to be split into three or four doses in order to avoid high peak levels of these drugs in the blood. Selection of AED assumes greater importance when there was a previous pregnancy with malformations in the fetus. Our policy, in such instances, is to use an alternate AED. If the patient had been seizure-free for more than six months, we attempt to switch over to monotherapy or reduce the dose of AED. AED dosage is increased when the patient has frequent generalized seizures or when the blood level of AED is considerably low.

Many patients and their families express their desire to postpone pregnancy until AEDs are withdrawn. General principles of AED withdrawal as applied to non-pregnant state are adopted for preconception and pregnancy period also. AED could be discontinued gradually if the patient had remained seizure-free for more than one or two years depending on the EEG findings except for Juvenile Myoclonic Epilepsy. This approach has its limitations for several reasons. The impact of increasing age of the mother, other co-morbidities and various other factors that aggravate maternal and fetal complications may nullify potential benefits of AED withdrawal. These aspects need to be discussed in detail with the patients and their families so that they can make well-informed decisions.

Management of pregnancy and delivery in women with epilepsy

Optimizing treatment of epilepsy

All WWE should attend to the gynaecologist for periodic antenatal check in addition to making consultations with the neurologist. As a general rule, the benefits of continuing AEDs need to be highlighted to the patients while discussing the possible hazards. It is worth reminding that most WWE have normal pregnancies and healthy babies even while on AEDs. However, there is a moderate increase in the risk of malformations in the baby. We can take several steps to minimize this risk (see Table 7).

It is useful to get blood level of AEDs, during each trimester of pregnancy. In the later part of pregnancy, the blood levels of AEDs tend to drop, although, this is not often accompanied by aggravation of seizures.

Folic acid prophylaxis

Although it is widely recognized that administration of folic acid reduces the risk of NTD in babies there is no consensus on the optimum dosage. WWE on enzyme inducing AEDs would need a higher dose. Women in India and other developing countries suffer the additional risk related to malnutrition and coexisting illnesses. Considering these facts we have adopted a dose of 5 mg of folic acid daily during pregnancy and the preconception period.

Screening for serious malformations in the fetus

Several non-invasive and invasive procedures can be utilized to screen the fetus for any serious congenital malformations.

Alfa feto protein. Estimation of Alfa feto protein (AFP) in maternal serum is a widely used screening test for

Table 6. Guidelines for pharmacotherapy of epilepsy in preconception period

Policy	Situation
Stop AED	Last seizure > 1 year, recent EEG Normal (except for JME)
	Last seizure > 2 years irrespective of EEG finding (except for JME)
Continue AED	JME even when seizure-free
	A seizure in the past one year
Monotherapy	If seizure-free for more than six months
Reduce AED	If seizure-free for more than six months
Increase AED	Frequent seizures

Table 7. Measures that can be adopted to reduce the risk of malformations in the baby

Early administration of folic acid
Switchover to monotherapy, if applicable
Use the least effective dose of the AED
Use smaller dosage multiple times per day rather than single large dose

Table 8. Normative data for serum AFP during normal pregnancy

Period of pregnancy (in weeks)	SAFP levels	SAFP levels
	Median	95th centile
15	29.8	56
16	32.2	60.6
17	37.1	69.8
18	42.3	79.6
19	51	96
20	60.5	113.9

antenatal detection of NTDs. Such screening should be undertaken between 12 and 18 weeks of pregnancy. AFP levels are typically elevated with open neural tube defects and to a lesser extent with spina bifida. Other anomalies such as congenital hydronephrosis, fetal distress, multiple pregnancies and fetoplacental hemorrhages also result in elevated levels of AFP. High levels of AFP should be interpreted carefully as errors in estimating gestational age, lack of laboratory standardization and several other factors can contribute to it. Estimation of precise conceptual age with an ultrasonograph and expression of AFP as multiples of median for the laboratory could eliminate some of these factors. The normative data for AFP in our program is given in Table 8.

Ultrasonography. The quality of the study depends to a large extent on careful preparation of the patient, the technical aspects and the expertise of the personnel who perform the test. The patient should be sufficiently relaxed and comfortable. A full bladder is useful to obtain a good window for echo. A vaginal probe may be helpful in early stages of pregnancy when the uterus is intrapelvic in location.

After 13–14 weeks the fetal profile can be seen in a sagittal view, showing development of the nose, mandible, maxilla as well as the orbit. The modified coronal view is useful to visualize cleft lip and cleft palate. NTD like anencephaly can be detected quite early in pregnancy. The fetal spine is clearly evaluated by 16 to 17 weeks of development. Spina bifida can be diagnosed when the posterior ossification centers splay outward and are further apart than the ossification centers above or below the defect. An intact sac of myelomeningocoele can also be seen. Scalloping of the frontal bones (lemon sign) and anterior curving of the cerebellar hemispheres with obliteration of cisterna magna (banana sign) are two other recently identified ultrasonographic features of open NTD. NTD and cleft lip/palate are frequently associated with polyhydramnios. Accordingly whenever poly or oligohydramnios is detected, a search for congenital anomalies should be done. Our protocol includes ultrasonography at 18 weeks.

Fetal cardiac echo is best performed after 16 weeks of gestation. By this time the valves are well developed, the size of heart is adequate for study and the fetal size and position usually allow best access to the heart. The long axis four-chamber view and short axis view help in delineating the cardiac anatomy. We do not routinely do fetal echocardiogram.

The sonologist should specifically look for commonly encountered malformations, as they are likely to be missed during a routine antenatal examination. Anatomic malformations are likely to grow during pregnancy just as the fetus does; a defect seen at birth may be too small to be detected earlier in pregnancy. Hence if there is a suspicion of congenital anomaly that could not be well visualized at 20–22 weeks, it is advisable to do more ultrasound examinations later in the 2nd and 3rd trimester.

Indications for medical termination of pregnancy

Pretest counseling addresses the role of screening tests for congenital malformations and the options available to the couple if a malformation is recognized by these tests. Psychological support and sympathetic counseling are very essential whenever a serious malformation is detected. If the family decides to terminate the pregnancy on grounds of serious, life incompatible malformations of the fetus, the details of the technique are decided by the attending obstetrician. Prostaglandin induction is avoided in WWE in view of its potential seizurogenic property.

Preterm vitamin K

Enzyme inducing AED therapy can cause vitamin K deficiency in neonates. Such babies may experience hemorrhagic disease of the newborn (HDN) that typically present between 2 and 7 days after delivery. All pregnant women are advised 10 mg vitamin K daily in the last month of pregnancy. In regions where oral preparations are not available, parenteral vitamin K is administered two injections of 10 mg each at 34 and 36 week of pregnancy. This does not supplant the recommended dose of 1 mg vitamin K to the neonate (see Figure 2).

Delivery

The gynaecologist plans the mode of delivery. Epilepsy by itself is not an indication for Caesarian section. Care is taken to ensure that AED is administered as per the schedule even while the patient is in the early stages of labour. If a breakthrough seizure occurs during labour, it is treated by intravenous diazepam. Serial generalized seizures are treated with intravenous PHT infusion. In several such cases, PHT could be withdrawn after the seizures were controlled.

Pregn: weeks	Date	Test	Fundal ht (wks)	FH	BP	Wt. (kg)
LMP						
8						
12						
16		SAFP				
18		USS				
20						
22						
24		TDM*				
26						
28						
30						
32		TDM*				
33						
34		Vit. K				
35						
36		Vit. K				
37						
38						
39						
40						
EDC		Neonatal exam				
3M		Echo				
12M		DQ				

SAFP, serum alpha feto protein; USS, ultrasound scan; TDM, Therapeutic drug monitoring (optional); Echo, Echocardiography, DQ, Development assessment.

Figure 3. Sample of patient diary used in KREP, Thiruvananthapuram.

Postpartum phase

Breastfeeding. The AED level in breast milk is inversely proportional to its protein binding property. AEDs like VPA appear only in trace amounts (2–3% of the blood levels) in breast milk whereas PHT (19%), PB (36%), CBZ (41%) and LTG (65%) appear in much greater concentration. All patients are encouraged to breastfeed their babies as its potential benefits far outweigh disadvantages. The dose of AED is not changed during the immediate post-partum period. However most patients would require a reduction in the dose of AED after two or three months.

Contraception. All mothers are informed about the need for spacing of pregnancy. Oral pills may be ineffective as enzyme inducing AEDs increase the metabolism of sex hormones. VPA and newer AEDs such as GBT, LTG, TBG and vigabatrine apparently do not have this disadvantage. Intrauterine devices or Medroxy progesterone depot preparations or barrier contraception are recommended in such patients. There is no contraindication for postpartum sterilization in WWE.

Neonatal evaluation. A careful clinical examination with special attention to any congenital anomaly or serious malformation is carried out on all newborns. Physiological status (apgar score at one minute and five minutes) and anthropometric measurements (head circumference, length, weight) are also recorded.

Echo and USS at 3 months. At three months all babies are subjected to ultrasound examination to exclude any hydrocephalus or intra-cerebral bleed (through anterior fontanel), internal malformation or visceral anomalies. An echocardiogram is also carried out then to exclude any congenital cardiac malformation.

Developmental assessment at one year. The protocol includes developmental assessment at one year and screening for learning disabilities or other subtle neurological impairments or epilepsy within five years of age. For the convenience of the patient and proper documentation of data, we have prepared a patient diary. It carries information on the patient, details of treatment and schedule of hospital visits and the seizure diary. See Figure 3.

Conclusion

There is a complex interaction between epilepsy, pregnancy and the effects of AEDs. It is reassuring to observe that the vast majority of pregnancies end in safe confinement and healthy babies. However, WWE deserve special medical attention during pregnancy and

delivery. An integrated service should ideally involve professionals in several medical specialties and social sciences.

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