

North Pacific Epilepsy Research Center

Antiepileptic Drug Use and Pregnancy

Mark S. Yerby M.D.
North Pacific Epilepsy Research
Portland, Oregon

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Introduction

There are approximately 1.1 million women of childbearing age in America with epilepsy. More sophisticated diagnostic techniques, effective medications, and improved training of neurologists in epilepsy care have given patients with epilepsy better opportunities for a full life and improved seizure control than ever before. In the recent past, persons with epilepsy were frequently discriminated against. There was a misperception that women with epilepsy should not marry or at least not have children. In fact, at one time most states had legislation prohibiting persons with epilepsy from marrying. Thankfully these laws have been repealed, but misunderstanding unfortunately persists.

Most women with epilepsy can and do have healthy, normal children. Over 90% of the time their children have no malformations, nor do they develop epilepsy. Most women have no change in their seizures during pregnancy or post partum complications. A small proportion of women with epilepsy will have difficulties conceiving and have complications with a pregnancy.

Increased Risks of Pregnancy for Women with Epilepsy

Effects on Epilepsy	Complications of Pregnancy	Complications in the Offspring
Increased seizure frequency	Vaginal hemorrhage	<u>Maldevelopment</u> Microcephaly Anomalies Malformations
Declining drug levels	Anemia Hyperemesis gravidarum	<u>Death</u> Stillbirth Neonatal death Perinatal death
Alteration of drug PK ^a	Toxemia	
	Induced labor	
	Premature rupture of membranes	Hemorrhagic disease
	Cesarean section	<u>Others</u> Low birth weight Prematurity Feeding difficulties Drug withdrawal Hypoxia
	Seizures	

^aPK=pharmacokinetics.

Conception

Infertility rates are higher in women with epilepsy than they are in the general population. While we do not have actual fertility rates epidemiological studies demonstrate that only 1/4 to 1/3 as many pregnancies occur in women with epilepsy as one would expect from their numbers in the population. It may be that as a group women with epilepsy are less likely to marry or if they do less likely to want to bear children. It may also be that women with epilepsy are less likely to report their disorder on birth certificates, which is where most of this information comes from. It appears however that women with epilepsy are more likely to have reproductive and endocrine problems. Several investigators have noted that women with epilepsy are more likely to have irregular menstrual periods, polycystic ovaries and hypogonadotropic hypogonadism.

It is unclear whether these problems are a result of epilepsy itself or the use of antiepileptic (AED), drugs. Menstrual cycles require the hypothalamic release of gonadotropin releasing hormones that stimulate the pituitary to release luteinizing and follicle stimulating hormones. These in turn effect the ovarian maturation and release of follicles. The sex steroid hormones estrogen and progesterone in turn have a "feedback" effect on the pituitary. Seizures can upset the hypothalamic pituitary ovarian axis. Prolactin a pituitary hormone is released in response to convulsions. Women with epilepsy may have lower pulse frequencies and concentrations of luteinizing hormone. Thus epilepsy itself could impair normal pituitary and ovarian function.

At least one Finnish investigator has described an increase rate of polycystic ovaries in women taking the anticonvulsant, valproic acid. At this time the cause and mechanism for the higher rates of infertility remain uncertain.

Maternal Seizures During Pregnancy

Though most women will have no change in their seizure rate when they become pregnant, approximately 1/4 to 1/3 will have an increase in seizure frequency. Though sleep deprivation and emotional stress can play important roles, changes in the metabolism of AED appear to be the primary cause of increased seizures in pregnancy. The concentrations of AED decline as pregnancy progresses even when doses are carefully maintained. There is a marked change in plasma protein binding resulting in higher proportions of free or unbound medication that is available for metabolism and clearance. Women are particularly vulnerable during the last portion of the third trimester and in the immediate post partum period. Monitoring the unbound AED concentrations and adjusting the dose to maintain therapeutic levels can reduce the risk of seizures.

Seizures during pregnancy are undesirable because they increase the risk of adverse pregnancy outcomes. Generalized convulsive seizures can induce premature labor and miscarriage, as well as increase the risk of falls and maternal injury. Seizures of any type increase the risk of the child having developmental delay as well as developing epilepsy.

Anticonvulsants and Pregnancy Outcome

The use of AED during pregnancy increases the risk of congenital malformations. The general population rate is 2-3%. The rate for infants of mothers with epilepsy (IME) is 4-6%. This risk has been associated with all of the older AED. The numbers of pregnancies in which newer AED have been used are still small enough that we are unable to assess accurate rates or risk.

It is believed that the mechanism whereby most AED cause malformations has to do with the development of reactive AED metabolites epoxides or free radicals. Medications that do not have epoxide or free radical metabolites may have safety

advantages over those that do not. Empirical evidence for this is lacking however.

Malformation risk appears to be higher in women treated with AED than those untreated. It is higher in women with high plasma concentrations of AED. Polytherapy with AED has higher malformation risk than monotherapy.

The types of malformations reported vary but there are some common themes. Oral facial clefts and midline heart defects, account for the majority of malformations. Limb defects particularly polydactyly, club foot and hypospadias are also frequently seen. In addition there are children who present with a variety of "minor" anomalies: hypertelorism, epicanthal folds, long philtrum, upturned nasal tip, full and prominent lips and small nails and poor ossification of the distal phalanges or distal digital hypoplasia. It occurs in less than 10% of children exposed to AED. Taken collectively children with these are said to have a "fetal anticonvulsant syndrome". It has been seen with all of the older AED. It is uncertain whether the newer medications will have this same risk. The significance of these anomalies is also uncertain. Developmental delay is associated with a large number of anomalies but many children appear to outgrow the dysmorphic features as they mature.

With certain AED (phenobarbital, phenytoin, primidone, and carbamazepine) there is a risk of neonatal hemorrhage. Rates are difficult to determine because the literature consists of case series but appears to be somewhat less than 7%. The hemorrhage occurs early within the first 24 hours of life and is internal thus often escaping detection until late. It is due to the fact that these AED are competitive inhibitors of prothrombin precursors. The competitive inhibition permits prevention of this disorder by maternal treatment with oral vitamin K, 10 mg. for the last week of pregnancy.

Specific Antiepilepsy Drugs

To simplify discussion of AED and risks in pregnancy we will divide AED into two groups: older drugs introduced before 1990; and newer drugs those introduced after 1990. Our experience is more extensive with the older AED. Carbamazepine, phenobarbital, phenytoin, primidone, ethosuximide, and valproic acid constitute this group. The plasma concentrations of all of them decline significantly during pregnancy, particularly for ethosuximide and phenobarbital which are weakly protein bound. All have been associated with an increased risk of malformations more so when used in polytherapy than monotherapy. The overall risk is 4-6%.

There are no head to head studies which would permit direct comparisons of these drugs, but there does not appear to be any significant difference in rates among these compounds. The exception is for the specific malformation spina bifida aperta. There is significant evidence that valproic acid exposure is associated with a 1-2% risk for this disorder. There is also an apparent dose response effect, in that there have been no reports of spina bifida in infants exposed to doses of less than 1000mg. a day. There is less solid evidence to suggest that carbamazepine is associated with a 0.5% risk of spina bifida. In women without epilepsy preconceptual folic acid has reduced the risk of spina bifida. The Center for Disease Control strongly recommends at least 0.4 mg. a day for all women of childbearing age. The mechanisms whereby women taking valproic acid have an increased risk of spina bifida are unknown and it is uncertain if folic acid is protective for these children.

The newer AED are: felbamate, gabapentine, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide. Though lamotrigine and oxcarbazepine have been used in Europe and zonisamide in Japan for at least 10 years there is little information available on their safety in pregnancy. The numbers of reported exposures are too small to calculate reliable rates of malformations. In addition because for all of these compounds the initial FDA approval was for adjunctive use, most pregnancies involve polytherapy and thus adverse outcomes cannot be assigned to a specific drug.

Here is what we know thus far.

Felbamate has been approved for use in the treatment of partial seizures. It is non oncogenic in rodents, and appears to be non teratogenic in rat and rabbit models. It unfortunately has a incidence of hepatic failure (1:18 to 25,000) and aplastic anemia (1: 4 to 5,000) and so the numbers of persons prescribed the drug is quite small. We know of only 9 pregnancies with no reported malformations.

Gabapentine though widely used as both adjunctive and monotherapy in partial epilepsy it appears to be even more commonly prescribed for pain and spasticity. Though developed as a GABA-mimetic that could easily cross the blood brain barrier, Gabapentine does not appear to act on GABA mediated systems. No teratogenicity has been found in rats or rabbits exposed to this drug. Mutagenic activity is absent in the Ames-Salmonella-Test, and in chromosome-metaphase analysis of hamster bone marrow. There is little data on its safety in pregnancy. In the clinical trials there were 16 pregnancies with 2 spontaneous, 5 elective abortions and one malformation (pyloric stenosis and an inguinal hernia). In the early post marketing period there were 32 reported pregnancies with 9 malformations all in polytherapy. With no data on the denominator (total number of exposures) malformation rates simply cannot be calculated. The lack of reactive metabolites suggests that gabapentine may be relatively safer than other AED.

Like many of the conventional AED, Lamotrigine also has mild antifolate activity. It appears to inhibit the release of excitatory amino acids such as glutamate, and is a potent anticonvulsant. Lamotrigine is non teratogenic in rats, and non mutagenic in bacterial and lymphocyte systems. It was initially introduced in Europe over 10 years ago and has had a pregnancy registry for a number of years. They have studied over 200 pregnancies with lamotrigine exposure. Most are with polytherapy. To date the numbers and types of malformations are similar to those seen with the older AED. Initial results from this registry have been submitted for publication and we will be able to examine the data soon.

Levetiracetam is the newest AED approved by the FDA in 2000. We therefore do not have any data on human pregnancies. It is recommended for use as adjunctive therapy in partial epilepsies in adults. It is not extensively metabolized and not by the hepatic cytochrome P-450 system. The primary metabolite is inactive. In rodent models minor skeletal abnormalities and decreased fetal weights have been described. Such animal models are not reliable predictors of human teratogenicity.

Oxcarbazepine differs from carbamazepine in that it contains a keto-group in the 10-11 position. This results in a significantly different metabolism into the 10-monohydroxy derivative (MHD). Since there is no 10-11 epoxide metabolite there appear to be fewer side effects, less allergic cross reactivity (27 %), but similar efficacy to carbamazepine. Whether it will also have less teratogenicity

is uncertain. In the first 12 reported cases of pregnancy with oxcarbazepine there have been 9 live births and 3 spontaneous abortions. In a prospective study of eleven pregnancies one child with spina bifida exposed to oxcarbazepine in polytherapy was reported. The manufacturer has been notified of 5 cases of fetal malformations in the post marketing period. One was a cardiac defect. There were 3 cleft palates and one facial dysmorphism. Three of the 5 were exposed to AED polytherapy. The drug has been available in Europe for 10 years, but an accurate denominator is not available thus we are unable to calculate rates.

Tigabine is a potent inhibitor of GABA reuptake into neurons and glia. It is a "designer" drug consisting of the potent anticonvulsant nipecotic acid joined to a lipophilic anchor which permits its passage across the blood brain barrier. No teratogenic effects in experimental animals have been noted. In the initial 23 reported pregnancies there have been: 9 live births; 6 miscarriages; 5 therapeutic abortions; 1 empty gestational sac, 1 C-section for breech presentation; one woman drowned while pregnant 3 months after stopping tiagabine therapy.

Topiramate is a potent compound for the treatment of partial seizures with or without secondary generalization, primarily generalized seizures, drop attacks in Lennox-Gastaut syndrome, and West's syndrome. It is a relatively new AED and we have no idea of the number of pregnancies with topiramate exposure. There is one case report of a child exposed to topiramate monotherapy who developed growth deficiency, hirsutism, a third fontanelle, and upturned nasal tip, and distal digital hypoplasia.

Zonisamide is a sulfonamide which has been demonstrated to block voltage sensitive sodium channels, voltage dependent calcium currents and suppress neuronal hyper synchronization. It is effective in partial and generalized seizures. It is taken up by erythrocytes binding to carbonic anhydrase. It has been widely prescribed in Japan for the past 10 years. There have been 26 reported pregnancies with zonisamide exposure. Two of the 26 (7.7%) had congenital malformations. One child was also exposed to phenytoin and the other to both phenytoin and valproic acid.

To improve our knowledge of the risks of AED particularly newer agents a North American Epilepsy and Pregnancy Registry has been established. Women with epilepsy who are pregnant are encouraged to call this toll free number to register 1 - 888 - 233 - 2334. The information collected will hopefully provide more accurate estimates of risk of AED exposure in utero.

Breast Feeding and AED Use

Breast feeding is highly recommended by most physicians. Women with epilepsy are often concerned about the safety of breast feeding with AED. Term infants have been exposed to AED for 9 months and will have had their hepatic microsomal enzyme systems induced. They can metabolize AED with the efficiency of adults and thus can usually breast feed with little difficulty. Occasionally phenobarbital and primidone may sedate a nursing infant and they fall asleep before becoming satiated. When such a pattern of frequent feeding with the infant falling asleep at the breast and shortly thereafter awakening hungry is seen breast feeding should stop. Most AED have breast milk concentrations lower than plasma.

Breast Milk / Plasma Concentrations of AED

<u>AED</u>	<u>Breast milk/ Plasma Concentration Ratio</u>	<u>Elimination 1/2 Life in Hours Adults</u>	<u>Elimination 1/2 Life in Hours Neonates</u>
Carbamazepine	0.4 - 0.6	8 - 25	8 - 28
Ethosuximide	0.9	40 - 60	40
Phenobarbital	0.4 - 0.6	75 - 126	45 - 500
Phenytoin	0.2 - 0.4	12 - 50	15 - 105
Primidone	0.7 - 0.9	4 - 12	7 - 60
Valproic Acid	0.01	6 - 18	30 - 60
Gabapentine	?	5 - 8	?
Felbamate	?	14 - 22	?
Lamotrigine	> 1.0	24	?
Levetiracetam	?	6 - 8	?
Oxcarbazepine	?	8 - 10	?
Tiagabine	?	4 - 13	?
Topiramate	< 1.0	19 - 23	?
Zonisamide	0.9	50 - 60	?

Conclusions

Seizures need to be prevented but fetal exposure to anticonvulsant drugs must be minimized. The ideal situation would be to withdraw the patient from anticonvulsants prior to conception. For most women, this is not a realistic option.

The major organ systems have formed by late in the first trimester. The posterior neuropore closes by day 27 and the palate by day 47 of gestation. By the time many women realize they are pregnant, malformations already may have developed. Changing AED at this point will not reduce the risk of such defects. Women with epilepsy of childbearing age need to be informed of the risks of pregnancy associated with anticonvulsant use prior to conception. They also need to know that seizures can be harmful to mother and fetus, but that risks can be reduced with proper care.

Risks can be minimized by the preconceptual use of multivitamins with folate, and using AEDs in monotherapy with the lowest effective dose. Supplementation with 0.4 mg/day of folate is recommended by the Center for Disease Control for all women of childbearing age with or without epilepsy. Monitoring free drug levels both prior to and during pregnancy will permit accurate assessment of concentrations in a situation where plasma protein binding is in flux. Dose adjustment, however, should be made on a clinical basis. Plasma anticonvulsant drug concentrations will fall in all pregnant women, but only one third will have an increase in seizures. Practitioners tend to keep dosage as low as possible during conception and organogenesis, but will often raise dosage during the third trimester to reduce the risk of seizures during labor.

Vitamin K₁ 10 mg/day should be initiated late in the third trimester to prevent neonatal hemorrhage. It is usually prescribed during the final month of gestation.

With good patient education and careful attention to preventive measures and seizure control women with epilepsy can look forward to even safer pregnancies and healthy children.

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