Risks and management of pregnancy in women with epilepsy

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ABSTRACT

Most women with epilepsy today can conceive and bear normal, healthy children, but their pregnancies present an increased risk for complications. Pregnancy can exacerbate seizure frequency in some women with epilepsy, and both maternal epilepsy and in utero exposure to antiepileptic drugs can increase the risk of adverse outcomes in children born to women with epilepsy. These outcomes include fetal loss and perinatal death, congenital malformations and anomalies, neonatal hemorrhage, low birth weight, developmental delay, and childhood epilepsy. After reviewing these risks, this article concludes with practical recommendations for reducing these risks and optimizing the management of pregnant women with epilepsy.

In the not-too-distant past, women with epilepsy were discouraged from childbearing and most states had laws prohibiting marriage for persons with epilepsy. Yet these attitudes have gradually given way to an atmosphere where marriage and motherhood are considered acceptable for women with epilepsy, and the management of pregnancy in women with epilepsy has gained increased attention from neurologists and other physicians.

The advent of better neurologic training, improved diagnostic techniques, and a host of effective antiepileptic drugs (AEDs) has vastly improved epilepsy management. Today, the majority of women with epilepsy can conceive and bear normal, healthy children. However, the pregnancies of women with epilepsy do present a greater risk for complications. Women with epilepsy may experience an exacerbation of their seizures during pregnancy, are more likely to have difficulties during labor, and have a higher risk of adverse pregnancy outcomes **(Table 1)**.

This article reviews the major risks that epilepsy and AEDs carry for pregnant women with epilepsy and their children. It concludes with recommendations for the management of pregnancy in women with epilepsy to minimize these risks and to avoid adverse outcomes in their offspring.

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PREGNANCY CAN INCREASE SEIZURE FREQUENCY

One quarter to one third of women with epilepsy have an increase in seizure frequency during pregnancy **(Table 2)**. This increase is unrelated to seizure type, duration of epilepsy, or seizure frequency during a previous pregnancy. While most studies have shown that the increase tends to occur toward the end of pregnancy, recent reports find that a substantial number of women (31%) experience this increase in the first trimester. In addition, of 215 prospectively studied pregnancies, 1 in 8 women (12.5%) had to be hospitalized because of complications from increased seizures during pregnancy.[1]

As pregnancy progresses, plasma concentrations, both total and unbound, of AEDs decline, even in the face of constant or, in some instances, increasing doses.[2–6] Plasma concentrations tend to rise postpartum.[7,8] Although reduction of plasma drug concentration is not always accompanied by an increase in seizure frequency, virtually all women with increased seizures in pregnancy have subtherapeutic drug levels.[9–13] The decline of AED levels during pregnancy

TABLE 1

See table 3 in Yerby MS, Epilepsia 2003; 44(suppl 3):33–40.

TABLE 2

Modified and updated from table 1 in Knight AH and Rhind EG, Epilepsia 1975; 16:99–110.

is largely a consequence of reduced plasma protein binding,[3,7,14] reduced albumin concentration, increased drug clearance,[2,10,15,16] and patient nonadherence. The clearance rates are greatest during the third trimester. **Table 3** summarizes select pharmacokinetic data for several AEDs when used in pregnant women.

EFFECTS OF SEIZURES DURING PREGNANCY

Seizures during pregnancy increase the risk of adverse pregnancy outcomes. Generalized tonic-clonic seizures increase the risk for hypoxia and acidosis,[17] as well as injury from blunt trauma. Canadian researchers have found that maternal seizures during gestation increase the risk of developmental delay.[18] Although rare, stillbirths have occurred following a single generalized convulsion[19,20] or series of seizures.[21] While it is uncommon, status epilepticus carries a high mortality rate for both mother and fetus. In a series of the 29 reported cases, 9 of the mothers and 14 of the fetuses died during or shortly after an episode of status epilepticus.[22] In another report, the child of a woman who had three generalized tonic-clonic seizures during her pregnancy (at 19, 28, and 32 weeks' gestation) developed an intracerebral hemorrhage in utero.[23]

Generalized seizures occurring during labor can have a profound effect on fetal heart rate.[24] The increased rate of neonatal hypoxia and low Apgar scores among infants born to epileptic mothers may

TABLE 3
Pharmacokinetic data for first-generation antiepileptic drugs when used in pregnant women

Antiepileptic drug	Decrease in total drug level by third trimester	Normal binding	Percent free fraction	
			Maternal	Neonatal
Carbamazepine	40%	22%	25%	35%
Ethosuximide	?	90%	?	?
Phenobarbital	55%	51%	58%	66%
Phenytoin	56%	9%	11%	13%
Primidone	55%	?	?	?
Derived phenobarbital	70%	75%	80%	?
Valproic acid	50%	9%	15%	19%

Data from reference 7 and from "Valproic acid disposition and protein binding in pregnancy," by Koerner M, et al, Ther Drug Monit 1989; 11:228–230.

be related to the occurrence of such seizures during labor.[25] Partial seizures do not appear to have an adverse effect on fetal heart rate.

OVERVIEW OF COMPLICATIONS IN THE OFFSPRING

The offspring of epileptic mothers are at heightened risk for a variety of adverse pregnancy outcomes, either from maternal epilepsy itself or from in utero exposure to AEDs. These complications include fetal loss and perinatal death, congenital malformations and anomalies, neonatal hemorrhage, low birth weight, developmental delay, and childhood epilepsy. The next several sections explore these risks to the children in some detail.

FETAL LOSS AND INFANT MORTALITY

Fetal death, defined as fetal loss after 20 weeks' gestation, appears to be as common and perhaps as great a problem as congenital malformations and anomalies. Studies comparing stillbirth rates found higher rates in infants of mothers with epilepsy (1.3% to 14.0%) than in infants of mothers without epilepsy (1.1% to 7.8%) **(Table 4)**.

Spontaneous abortion, defined as fetal loss prior to 20 weeks' gestation, appears to occur more commonly in infants of mothers with epilepsy.[26] Women with localization-related epilepsies appear to be at greater risk for spontaneous abortions than those with other epilepsy syndromes.[27]

Other studies have demonstrated increased rates of neonatal and perinatal death. Neonatal death rates range from 1.3% to 7.8%, compared with 1.0% to 3.9% for controls **(Table 4)**.

CONGENITAL MALFORMATIONS

Congenital fetal malformations and anomalies have been associated with in utero exposure to AEDs. *Congenital malformations* are physical defects requiring medical or surgical intervention and resulting in a major functional disturbance. *Congenital anomalies*, in contrast, are deviations from normal morphology that do not require intervention. It is uncertain whether these aberrations represent distinct entities or a spectrum of physiologic responses to insult to the developing fetus, with malformations at one end and anomalies at the other. In this review, congenital malformations and anomalies will be discussed separately.

Infants of mothers with epilepsy exposed to AEDs in utero are twice as likely to have birth defects as infants not exposed to these drugs. Whereas malformation rates in the general population range from 2% to 3%, reported malformation rates in populations of AED-exposed infants range from 1.25% to 11.5%.[16,28–33] When combined, this range of estimates for exposed infants yields a 4% to 6% risk of malformation in a pregnancy of a woman with epilepsy. Cleft lip, cleft palate, or both, along with congenital heart disease, account for many of the reported cases. Orofacial clefts constitute 30% of malformations in these infants.[29,34,35]

In one report, first-trimester seizures were associated with a 12.3% risk of congenital malformations in offspring, compared with a 4% risk among offspring exposed to maternal seizures at other times.[36]

TABLE 4
Stillbirth and neonatal death rates in infants of women with epilepsy

Investigators	Stillbirths (%)		Neonatal deaths (%)	
	Cases	Controls	Cases	Controls
Janz, 1964	12.1	7.0	1.3	—
Speidel and Meadow, 1972	1.3	1.2	2.7	1.0
Bjenkdal and Bahna, 1973	5.3	7.8	3.2	1.5
Fedrick, 1973	2.7	1.1	—	—
Higgins and Comertond, 1974	5.2	—	7.8	3.9
Knight and Rhind, 1975	2.0	—	2.9	—
Nakane, 1979	13.5	4.3	—	—
Nakane, 1980	14.0	6.7	—	—
Nelson and Ellenberg, 1982	5.1	1.9	3.5	2.7
Svigos, 1984	0	1.3	—	—
Kalen, 1986	2.2	—	2.7	—
Tanganelli and Regesta, 1992	—	—	2.2	1.4

Neural tube defects: a possible pattern of causality

A wide variety of congenital malformations have been reported, and every AED has been implicated as a cause. No AED can be considered absolutely safe in pregnancy, yet most of these drugs do not produce any specific pattern of major malformations. Possible exceptions, however, are sodium valproate and carbamazepine, which have been associated with neural tube defects (NTDs).

Robert and Guibaud[37] first made this association when, working on a birth defects registry in the Rhône-Alps region of France, they reported NTDs in infants of mothers with epilepsy exposed to valproic acid in utero. Between August 1979 and August 1982, 72 infants with lumbosacral NTDs were born in this region. Nine of the 72, or 12.5%, had been exposed to valproic acid. Two of these 9 infants had a family history of NTDs; among the others, 5 were exposed to valproate monotherapy, 1 to valproate and phenobarbital, and 1 to valproate and clonazepam.

To clarify this observation, Robert et al[38] studied another 141 pregnancies in women with epilepsy, using a combination of questionnaires and electroencephalogram registries. This unselected cohort had a malformation rate of 17.7% and 4 cases of spina bifida (all with intrauterine exposure to valproic acid, though only 1 with monotherapy).

More-recent studies have revealed an association between in utero carbamazepine exposure and NTDs.[39,40] Subsequent evaluations of these exposures identify spina bifida aperta as the specific NTD associated with the valproic acid or carbamazepine exposure.[36] Problems with methodology make frequency estimates imprecise; most published data are from case reports, case series, or very small cohorts from registries not designed to evaluate pregnancy outcomes.

The prevalence of spina bifida aperta (SBA) is approximately 1% to 2% with valproate exposure[41] and 0.5%[39,42] with carbamazepine exposure. However, a prospective study in the Netherlands[36] found that infants of mothers with epilepsy exposed to valproate had a 5.4% prevalence of SBA. The average daily valproate doses were higher in mothers of infants with SBA (1,640 ± 136 mg/day) than in mothers of unaffected infants (941 ± 48 mg/day). Other investigators have found that valproate doses of 1,000 mg/day or plasma concentrations of 70 µg/mL or less are unlikely to cause malformations.[33] Both groups recommend that the dose be reduced in cases where valproate must be used in pregnancy.[33,43] Increasing dose frequency may also help reduce high peak concentrations when valproate must be used.

Pathophysiology of neural tube defects

NTDs are uncommon, occurring in 6 in 10,000 pregnancies. Spina bifida and anencephaly, the most commonly reported NTDs, affect approximately 4,000 pregnancies annually, resulting in 2,500 to 3,000 affected births in the United States each year.[44,45] The types of NTDs associated with AED exposure are primarily myelomeningocele and anencephaly, which are the result of abnormal neural tube closure between gestational weeks 3 and 4.

A number of risk factors are associated with NTDs. A previous pregnancy resulting in offspring with an NTD carries the strongest association, with a relative risk of 10. There also are strong ethnic and geographic correlations with NTDs. Rates per 1,000 births are 0.22 for whites, 0.58 for persons of Hispanic descent, and 0.08 for persons of African descent.[46] The incidence of NTDs in offspring is 3.26 per 1,000 for women in Mexico, 1.6 per 1,000

for Mexican-born women living in California, and 0.68 per 1,000 for US-born women of Mexican descent.[46] Children born to diabetic mothers are 7.9 times as likely as the general population to have NTDs.[47] Deficiencies of glutathione, folate, vitamin C, riboflavin, zinc, cyanocobalamin, and selenium have also been associated with NTDs, as has excessive exposure to vitamin A. Elevated rates of NTDs are seen in children of farmers, cleaning women, and nurses.[48,49]

Prepregnancy weight has also been shown to be a factor. Using women weighing 50 to 59 kg as controls, Werler et al[50] found that women weighing 80 to 89 kg had a 1.9 relative risk for NTDs in their offspring and women weighing 110 kg or more had a relative risk of 4.0.

AEDs may be a necessary but not a sufficient risk factor for the development of NTDs. Therefore, it is possible that AED treatment may increase the risk in women with one or more of the other risk factors discussed above. However, the possible teratogenicity of AEDs themselves cannot be completely ruled out.

Folate deficiency as a potential mechanism of AED teratogenicity

Folate is a coenzyme necessary for the development of red and white blood cells and for proper function of the central nervous system. Normal concentrations are typically measured in the serum (normal serum folate = 6 to 20 ng/mL) and erythrocytes (normal red blood cell folate = 160 to 640 ng/mL). Folate deficiencies have been implicated in the development of birth defects. Low levels of serum folate (< 6.6 ng/mL) and red blood cell folate (< 140 ng/mL) are associated with hyperhomocystinemia, which may be associated with NTDs. Dansky et al[51] found significantly lower blood folate levels in epileptic women with abnormal pregnancy outcomes compared with those who had normal outcomes.

Eight interventional trials have shown that preconceptual folate reduces the risk of malformations, NTDs, and NTD recurrence in women with a prior affected pregnancy. Biale and Lewenthal[52] reported a 15% malformation rate in infants of epileptic mothers who received no folate supplementation, whereas no abnormalities occurred in 33 infants born to epileptic women who did receive folate supplementation. Cotreatment of mice with folic acid, with or without vitamins and amino acids, also reduced malformation rates and increased fetal weight and length in mice pups exposed to phenytoin in utero.[53]

Unfortunately, preconceptual folate supplementation may not be protective for women with epilepsy. Craig et al[54] reported a young woman whose seizures were controlled for 4 years by 2,000 mg/day of valproic acid. Although she took 4.0 mg/day of folic acid for 18 months before her pregnancy, she delivered a child with a lumbosacral NTD, a ventricular and atrial septal defect, a cleft palate, and bilateral talipes. Duncan et al[55] reported two Canadian women who delivered children with NTDs despite folate supplementation. One of the women, who took 1,250 mg of valproic acid supplemented by 3.5 mg of folic acid for 3 months before conception, aborted a child with lumbosacral spina bifida, Arnold-Chiari malformation, and hydrocephalus. The second woman, also on valproic acid, took 5 mg of folic acid but still had one spontaneous abortion of a fetus with an encephalocele and two therapeutic abortions of fetuses with lumbosacral spina bifida.

Not all research supports an association between folate deficiency and fetal malformations. Mills et al[56] found no difference in serum folate levels between mothers of children with NTDs and controls. A number of other studies have failed to demonstrate a protective effect for preconceptual folate,[57–62] but these studies are problematic because of small sample sizes, failure to document folate supplementation, or recall bias in the retrospective investigations. In addition, genetic and racial predisposition to NTDs was not accounted for.

The utility of folate supplementation for the general population is clearly established. Women with epilepsy, like all women of childbearing age, should take folate supplements, but it remains unclear whether this will reduce the risk of birth defects in the children of those women taking AEDs. The recommended daily allowances of folate have been raised to 400 µg/day for nonpregnant women, 600 µg/day for pregnant women, and 500 µg/day for lactating women. Increased folate catabolism during pregnancy, together with variations in requirements among individual women, has led some to call for higher folate supplementation, on the order of 500 to 600 µg/day.[63] The 400-µg/day dose recommended by the Centers for Disease Control and Prevention (CDC) may not be high enough for many women who do not metabolize folate effectively. Even with folate supplementation, women taking valproate or carbamazepine should avail themselves of prenatal diagnostic ultrasonography to rule out NTDs.

Other possible mechanisms of AED teratogenicity

Over the last 15 years, a body of evidence has accumulated supporting the following hypotheses:

- An arene oxide metabolite of phenytoin or other AEDs is the ultimate teratogen
- A genetic defect in epoxide hydrolase (the enzyme system that detoxifies arene oxides) increases the risk of fetal toxicity
- Free radicals produced by AED metabolism are cytotoxic
- A genetic defect in free radical scavenging enzyme activity increases the risk of fetal toxicity.

Epoxides. A large number of drugs and chemicals can be converted into epoxides; these reactions are catalyzed by the microsomal monoxygenase system.[64,65] Arene oxides are unstable epoxides formed by aromatic compounds. Various epoxides are electrophilic and may elicit carcinogenic, mutagenic, and other toxic effects by covalent binding to critical cell macromolecules.[66,67] Epoxides are detoxified by two types of processes: (1) conversion to dihydrodiols catalyzed by epoxide hydrolase in the cytoplasm, and (2) conjugation with glutathione in the microsomes (spontaneous or mediated by glutathione transferase). Epoxide hydrolase activity has been found in the cytosol and the microsomal subcellular fraction of adult and fetal human hepatocytes. Interestingly, epoxide hydrolase activity is much lower in fetal livers than in adult livers.[68] One third to one half of fetal circulation bypasses the liver, resulting in higher direct exposure of extrahepatic fetal organs to potential toxic metabolites.[69]

These facts cannot completely explain the teratogenicity seen with phenytoin or other AEDs. The lymphocyte cytotoxicity seen with epoxide metabolites correlates with major but not minor malformations.[51] Although dysmorphic abnormalities have been described in siblings exposed to ethotoin in utero, ethotoin is not metabolized through an arene oxide intermediate.[70] Similarly, embryopathies have been described with exposure to mephenytoin, which also does not form an arene oxide intermediate.[71] Finally, trimethadione is clearly teratogenic but has no phenyl rings and thus cannot form an arene oxide metabolite. Therefore, an alternative mechanism must exist.

Free radical intermediates of AEDs and teratogenicity. Some drugs are metabolized or bioactivated by co-oxidation during the prostaglandin synthetase–catalyzed synthesis of prostaglandins. Such drugs serve as electron donors to peroxidases, resulting in an electron-deficient drug molecule, which by definition is called a free radical. In the search for additional electrons to complete their outer ring, free radicals can covalently bind to cell macromolecules—including nucleic acids (DNA, RNA), proteins, cell membranes, and lipoproteins—to produce cytotoxicity.

SYNDROMES OF CONGENITAL ANOMALIES

In contrast to malformations, which are anatomic deformities requiring intervention to maintain functional health, anomalies are abnormalities of structure that do not constitute a threat to health. Patterns of anomalies in infants of mothers with epilepsy have been noted with exposure to certain AEDs. Five clinical syndromes have been reported in infants of mothers with epilepsy: fetal trimethadione syndrome, fetal hydantoin syndrome, primidone embryopathy, fetal valproate syndrome, and fetal carbamazepine syndrome. Dysmorphic facial features have also been described in infants of mothers taking benzodiazepines or lamotrigine. Clinically, these syndromes primarily involve dysmorphic features of the midface. Moore et al[72] suggest that learning and behavior disturbances are an important aspect of these syndromic anomalies. In an unselected cohort of 52 affected children, 77% were found to have developmental delay, 81% to have autistic behaviors, and 39% to be hyperactive.[72]

Clinical and laboratory evidence clearly supports the association of certain AEDs with teratogenic effects, particularly facial and distal digital anomalies. However, the existence of drug-specific syndromes is doubtful. Facial dysmorphism is difficult to quantify and clearly not drug-specific. Infants of epileptic mothers with similar dysmorphic features were described in the preanticonvulsant era.[16,73] Follow-up of these infants into adulthood has yet to be accomplished, so the significance of these anomalies is unclear. Gaily et al[74] followed a cohort of infants of mothers with epilepsy to 5 1/2 years of age. Compared with control children, these children had an excess of minor anomalies characteristic of fetal hydantoin syndrome, but so did their mothers relative to control mothers. Only hypertelorism and digital hypoplasia were associated with phenytoin exposure. Certain anomalies, particularly epicanthal folds, appeared to be associated with maternal epilepsy, not with AED exposure.

The hypothesized association of dysmorphic features with mental retardation[29] has not been con-

firmed. In the few cases that have been followed into early childhood, the dysmorphic features tended to disappear as the child grew older.[10] Mental deficiency was found in only 1.4% of infants of mothers with epilepsy followed to 5 1/2 years of age.[75] Exposure to AEDs below toxic concentrations or to maternal seizures did not increase the risk of lower intelligence. No association between features of fetal hydantoin syndrome and mental retardation could be demonstrated.

The primary abnormalities in these syndromes involve the midface and distal digits. In a retrospective study spanning 10 years of deliveries in Israel, hypertelorism was the only anomaly seen more often in infants of mothers with epilepsy than in controls.[76] This anomaly was associated with all AEDs except primidone. A prospective study of 172 deliveries of infants of mothers with epilepsy evaluated eight specific AEDs and other potential confounding factors and found no dose-dependent increase in the incidence of malformations with any individual AED. Furthermore, no specific defect could be associated with individual AED exposure.[77] It has been suggested that, since a variety of similar anomalies of the midface and distal digits are seen in a small proportion of children exposed to AEDs in utero, a better term for the entire group of abnormalities would be *fetal anticonvulsant syndrome* or *AED embryopathy*.[78–80]

NEONATAL HEMORRHAGE

For many years it has been reported that infants of mothers with epilepsy are at increased risk for a unique form of neonatal hemorrhage. First described by Van Creveld,[81] who suggested that vitamin K deficiency might be the cause, it was first delineated as a syndrome by Mountain et al,[82] but there have been numerous reports of in utero AED exposure associated with neonatal hemorrhage.[83–89] It was initially associated with exposure to phenobarbital or primidone but has subsequently also been described in infants exposed to phenytoin, carbamazepine, diazepam, mephobarbital, amobarbital, and ethosuximide.

It has been differentiated from other hemorrhagic disorders in infancy in that the bleeding occurs internally, during the first 24 hours of life. Accurate prevalence figures are not available.

The hemorrhage appears to result from a deficiency of vitamin K–dependent clotting factors II, VII, IX, and X. Maternal coagulation measures are invariably normal. The fetus, however, will demonstrate diminished clotting factors and prolonged prothrombin and partial thromboplastin times. A prothrombin precursor, protein induced by vitamin K absence (PIVKA), has been discovered in the serum of mothers taking anticonvulsants.[90] Assays for PIVKA may permit prenatal identification of infants at risk for hemorrhage.[91,92]

The historical demonstration of an increased risk of neonatal hemorrhage, coupled with a demonstrated deficiency of vitamin K and the PIVKA findings, led clinicians to believe that the relative lack of vitamin K and the presence of PIVKA was the cause of this particular neonatal hemorrhage. Several studies demonstrated that oral maternal supplementation increased neonatal vitamin K and reduced hemorrhage.[93–95]

This practice has been challenged, however. Kaaja et al[96] found no difference in rates of neonatal hemorrhage between 667 infants of mothers with epilepsy (0.7%) and 1,334 control infants (0.4%). No mothers in either group received vitamin K supplementation, but all infants received intramuscular vitamin K at delivery. These researchers felt that no evidence of a difference in clinical bleeding could be found, so supplementation was not recommended. Hey[97] measured cord blood from 137 infants of mothers with epilepsy taking phenobarbital, phenytoin, or carbamazepine and found that 14 of 105 had prolonged prothrombin times but none had any clinical bleeding. He concluded that the lack of clinical bleeding in his series made vitamin K supplementation inappropriate.

The problem, in part, is that there is confusion between vitamin K deficiency, laboratory evidence of abnormal coagulation measures, and clinical bleeding. Vitamin K deficiency is common, the presence of PIVKA less so, but clinical bleeding in neonatal life is rare. Shapiro et al[98] demonstrated that PIVKA presence is fairly uncommon in the general population of newborns (2.9%) and more common in premature infants. We have no good data on the prevalence of neonatal hemorrhage in infants of mothers with epilepsy, but we do have reasonably accurate case reports.

We also have reasonable causation. AEDs can act like warfarin and can inhibit vitamin K transport across the placenta. These effects can be overcome by large concentrations of the vitamin. Despite lower coagulation factor levels, the fetus is generally able to obtain enough maternal vitamin K

in utero. After birth, the infant must rely on exogenous sources of vitamin K because the newborn gut is sterile. Routine administration of vitamin K at birth is not adequate to prevent hemorrhage if any two of the coagulation factors fall below 5% of normal values.[89] Successful treatment requires fresh frozen plasma intravenously.

It is clear that vitamin K supplementation should be offered to pregnant women with epilepsy. The risk of neonatal hemorrhage, while low, clearly exists, as demonstrated by elevated PIVKA levels, particularly in women taking enzyme-inducing AEDs. There is no effective intervention once a neonate bleeds. Also, there is the possibility of small bleeds that, while not clinically detectable at birth, may have long-term effects. Moreover, vitamin K supplementation at the recommended level (10 mg/day) poses no risk. There is also a clear need for better prevalence data on the true risk of clinical bleeding in infants of mothers with epilepsy.

LOW BIRTH WEIGHT

Low birth weight (< 2,500 g) and prematurity have been described in infants of mothers with epilepsy. The average rates range from 7% to 10% for low birth weight and 4% to 11% for prematurity.[24,30,99–101] These studies do not analyze the effects of specific seizure types, seizure frequency, or AEDs on this aspect of fetal development.

DEVELOPMENTAL DELAY

Infants of mothers with epilepsy have been reported to have higher rates of mental retardation than controls; the risk is increased twofold to sevenfold, according to various authors.[102] None of these studies controlled for parental intelligence, however. Differences in Full Scale Intelligence Quotient (FSIQ) scores at age 7 between groups of children exposed (FSIQ = 91.7) or not exposed (FSIQ = 96.8) to phenytoin reach statistical significance, but the clinical significance of these differences is unknown.[103]

We have found that infants of mothers with epilepsy score lower on measures of verbal acquisition at both 2 and 3 years of age. Though there was no difference in physical growth measures between infants of mothers with epilepsy and controls, infants of mothers with epilepsy scored significantly lower on the Bayley Scale of Infant Development's mental developmental index at 2 and 3 years. They also performed significantly less well on the Bates Bretherton early language inventory ($P \leq .02$) and on the Peabody Picture Vocabulary scales of verbal reasoning ($P \leq .001$) and composite IQ ($P \leq .01$). They also demonstrated significantly shorter mean lengths of utterance ($P \leq .001$).[104]

Infants exposed to AED polytherapy performed significantly less well on neuropsychometric testing than did those exposed to monotherapy. Socioeconomic status had the strongest association with poor test scores, but maternal seizures during pregnancy were also a significant risk factor.[105]

Leonard et al[18] have partially addressed the question of whether maternal seizures or in utero exposure to AEDs is responsible for the developmental delays seen. A group of children of mothers with epilepsy followed to school age were found to have a rate of intellectual deficiency of 8.6%. The Wechsler Intelligence Scale for Children showed significantly lower scores for children exposed to seizures during gestation (100.3) than for children whose mothers' seizures were controlled (104.1) or for controls (112.9). All AEDs are clearly not created equal in this respect, and Koch et al[106] have demonstrated that primidone, particularly when used in polytherapy, is associated with lower Wechsler Intelligence Scale scores.

EPILEPSY IN THE CHILDREN OF EPILEPTIC PARENTS

The risk of epilepsy in children of parents with epilepsy is higher than that in the general population. Interestingly, this risk is higher for children of mothers with epilepsy (relative risk = 3.2).[107] Paternal epilepsy appears to have less impact on the development of seizures in children. The presence of maternal seizures during pregnancy is associated with an increased risk of seizures in the offspring (relative risk = 2.4),[108] although AED use is not. Evidence to support a genetic component for seizure development in these infants comes from kindling studies in experimental animals. If rats with experimental epilepsy are made to have generalized seizures during pregnancy, their offspring are not more susceptible to kindling than the offspring of rats with no seizures during parturition.[109]

PROFILE OF SPECIFIC EFFECTS OF NEWER AEDs IN PREGNANCY

A number of new AEDs have been marketed in the United States since 1993: gabapentin, felbamate, lamotrigine, levetiracetam, oxcarbazepine, tiaga-

bine, topiramate, and zonisamide. The number of reported pregnancies exposed to these drugs is very low, and not large enough to determine if there is an increased risk of adverse outcome with fetal exposure. We know that lamotrigine and levetiracetam concentrations decline during pregnancy and expect that this is also true for the other newer AEDs.[5,6] The paragraphs below summarize currently available data on the use of specific newer AEDs in pregnancy.

Gabapentin

A study combining retrospectively and prospectively collected cases evaluated 44 children born to 39 mothers with epilepsy taking gabapentin. Two of 44 (4.5%) had major malformations. One child exposed to gabapentin and valproic acid had hypospadias. The other, exposed to gabapentin monotherapy until the 16th week of gestation and then to phenobarbital, had only one kidney.[110]

Lamotrigine

The International Lamotrigine Pregnancy Registry has identified 334 pregnancies in women taking lamotrigine during the first trimester. Of these pregnancies, 168 were exposed to monotherapy and 166 to polytherapy. There is a difference in malformation rates when lamotrigine is used as monotherapy (1.8%), as polytherapy with valproic acid (10%), or as polytherapy without valproic acid (4.3%). The three reported malformations attributed to monotherapy in this prospective registry were esophageal malformation, cleft palate, and club foot.[111]

Lamotrigine crosses the placenta. At birth, mother and fetus have similar plasma concentrations. Elimination in infants appears to be rather slow. At 72 hours postpartum, infant plasma levels are 75% those of the mother. Median milk-to-plasma ratios are 0.61.[8]

Oxcarbazepine

The first 12 reported cases of pregnancy with oxcarbazepine resulted in 9 live births and 3 spontaneous abortions. In a prospective study of 11 pregnancies, the birth of 1 child with spina bifida exposed to oxcarbazepine as part of polytherapy was reported.[112] The only prospective series reported to date evaluated 42 oxcarbazepine-exposed pregnancies in Buenos Aires.[113] There were no malformations in the 25 monotherapy-exposed children. One child exposed to oxcarbazepine and phenobarbital had a ventricular septal defect.

Oxcarbazepine crosses the placenta, and maternal and fetal cord levels are equivalent.[114]

Topiramate

We have little information on the number of pregnancies exposed to topiramate. There is one case report of a child exposed in utero to topiramate monotherapy who developed growth deficiency, hirsutism, a third fontanelle, an upturned nasal tip, and distal digital hypoplasia. During clinical trials, 28 pregnancies were reported, with 1 malformation and 2 anomalies. The manufacturer has collected data on 139 pregnancies during postmarketing surveillance. Of these, 87 resulted in live births, 29 were lost to follow-up, and 23 were therapeutically aborted. There were 5 cases of hypospadias [personal communication at the Finnish Epilepsy Society annual meeting, 2002].

Topiramate crosses the placenta, and cord and maternal plasma levels are equivalent at delivery. Milk-to-plasma ratios average 0.86. Infant elimination appears to be substantial, with little measurable drug found in the plasma of breast-fed infants 2 to 3 weeks postpartum.[115]

Zonisamide

Twenty-six pregnancies with zonisamide exposure have been reported. Two of the 26 (7.7%) involved congenital malformations: one child was also exposed to phenytoin, and the other to both phenytoin and valproic acid.[116]

Zonisamide freely crosses the placenta, with transfer rates of 92%. Though data are available from only 2 children, milk-to-plasma ratios are 0.8 and the elimination half-life ranges from 61 to 102 hours.[117]

EFFECTS OF VAGUS NERVE STIMULATION

Vagus nerve stimulation is a technique that uses an implanted generator to produce electrical stimulation of the left vagal nerve, in the neck. The device, manufactured by Cyberonics Corp., Houston, Tex., is used to reduce the frequency and severity of seizures. Approximately 13,000 persons with epilepsy have had the device implanted. There have been 11 pregnancies in epileptic women using the device. Eight had normal children. Two women chose to have elective abortions, and one of these fetuses was malformed, arguably from the AED that the woman was also taking. One woman had a spontaneous abortion.[118]

TABLE 5
Antiepileptic drug pharmacokinetics in plasma and breast milk

Antiepileptic drug	Protein binding (%)	Half-life (hr)		Milk-to-plasma ratio
		Adult	Neonate	
Carbamazepine	75	8–25	8–28	0.4–0.6
Ethosuximide	<10	40–60	40	0.9
Felbamate	25	14–22	?	?
Gabapentin	0	5–8	?	?
Lamotrigine	55	24	?	0.4–0.7
Levetiracetam	<10	6–8	?	?
Oxcarbazepine	45	8–10	?	?
Phenobarbital	45	75–126	45–500	0.4–0.6
Phenytoin	90	12–50	15–105	0.2–0.4
Primidone	<20	?	?	0.7–0.9
Tiagabine	95	4.5–13	?	?
Topiramate	15	19–23	?	0.86
Vigabatrin	0	5–8	?	?
Zonisamide	50–60	63	?	0.8

RECOMMENDATIONS FOR MANAGING THE PREGNANT WOMAN WITH EPILEPSY

Those who care for pregnant women with epilepsy face a dilemma. Seizures must be prevented, but fetal exposure to AEDs must also be minimized. Although it might seem ideal to withdraw the patient from AEDs before conception, for most women this is not a realistic option. Women today are more likely to be employed, and the potential disruption of their lives by seizures (eg, the risk of losing one's driver's license) makes elimination of AEDs impractical. More importantly, maternal seizures increase the risk of injury, of miscarriage, and of epilepsy and developmental delay in the offspring.

By late in the first trimester, the major organ systems have formed. The posterior neuropore closes by the 27th day of gestation, and the palate by the 47th day. By the time most women realize that they are pregnant, malformations already may have developed. Epileptic women of childbearing age need to be informed of the risks associated with AED use **(Table 1)** prior to conception, if at all possible. They also need to know that seizures can be harmful to mother and fetus, and that risks can be reduced with proper care.

General recommendations for risk reduction

Even healthy parents have a 2% to 3% risk of having a child with a malformation. Given the current state of the art, the best we can do is practice risk reduction. In general, risks can be minimized by the preconceptual use of multivitamins with folate, by using AEDs in monotherapy at the lowest effective dose, and by preventing maternal seizures. Monitoring free drug levels both before 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 AED concentrations will fall in all pregnant women, but only one fourth to one third of pregnant women will have an increase in seizures. We tend to keep the dosage as low as possible during conception and organogenesis, but will often raise it during the third trimester to reduce the risk of seizures during labor.

Vitamin supplementation

Supplementation with at least 0.4 mg/day of folate is recommended by the CDC for all women of childbearing age, whether or not they have epilepsy. Recent studies have suggested that 0.5 or 0.6 mg/day might be more effective. For women with a family history of an NTD, 4.0 mg/day is the recommended dose. A number of observational and interventional studies have demonstrated a reduction in the risk of malformations in general, and of NTDs in particular, in women taking folate prior to conception.[57,59,119–121] The doses used in these studies ranged from 0.36 to 5.0 mg/day.

Vitamin K_1, at a dose of 10 mg/day, should be initiated late in the third trimester to prevent neonatal hemorrhage. We usually prescribe it during the final month of gestation.

Breast-feeding

Breast-feeding is generally safe in term infants, as they have been exposed to the mother's AED for 9 months and their hepatic microsomal enzyme systems have been induced. However, breast-feeding should be undertaken cautiously by women receiving phenobarbital or primidone because of the risk of infant sedation. The known milk-to-plasma concentration ratios of AEDs are listed in **Table 5**.

Prenatal diagnostic techniques

Pregnant women taking valproate, carbamazepine, or both should avail themselves of prenatal ultrasonography and alpha-fetoprotein measurement. Ultrasonography has become much more accurate and, in experienced hands, can identify the vast majority of structural defects. Current prenatal testing recommendations are as follows:

- Anatomic ultrasonography at 11 to 13 weeks to identify the most severe defects, such as anencephaly
- Maternal serum alpha fetoprotein
- Repeat anatomic ultrasonography at 16 weeks to identify abnormalities such as orofacial clefts, heart defects, and caudal NTDs.

Create a plan based on gestational age

When a pregnant women with epilepsy initially presents to her neurologist, the gestational age of the fetus must be established with reasonable accuracy. One cannot rely on the last menstrual period alone; an early ultrasonogram should be obtained to date the pregnancy. Once gestational age is established, a calendar can be planned, with dates determined ahead of time for monthly AED level checks, prenatal testing, and initiating vitamin K supplementation.

Managing more than just seizures

The management of pregnant women with epilepsy presents unique challenges. Confirmation of the diagnosis of epilepsy and verification of the most appropriate AED for the individual are the starting points. With effective patient education and careful and consistent management—which includes coordinated treatment planning by both neurologist and obstetrician—these patients can and do have successful pregnancies and healthy offspring.

NTDs are serious malformations for which there are no effective therapeutic interventions. Their risk can be reduced by careful management and theoretically may be eliminated by prenatal diagnosis and therapeutic abortion. In our role as advisors, clinicians need to recognize that all patients may not share our value systems or even begin to perceive what it really means to care for a child with an NTD. We must be sensitive to our patients' anxieties and be prepared to manage both their seizures and their emotional concerns.

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