

## Using Current Evidence in Selecting Antiepileptic Drugs for Use During Pregnancy

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*Children born to mothers taking antiepileptic drugs (AEDs) are at increased risk for findings of fetal anticonvulsant syndrome. Accepted treatment paradigms to minimize fetal risks include use of AED monotherapy and folic acid supplementation. However, as data are acquired from several ongoing pregnancy registries, differential risks among the various AED monotherapy regimens are being defined, further improving fetal outcomes.*

Prescription of antiepileptic drugs (AEDs) to women with epilepsy during the reproductive years requires maintaining a precarious balance between controlling seizures and minimizing fetal exposure to harmful effects of the medications. Epilepsy is the most common neurologic disorder that requires continuous treatment during pregnancy, and AEDs are among the most frequently administered prolonged teratogen exposures (1,2). Fetal anticonvulsant syndrome consists of various combinations of the following features: minor anomalies, major congenital malformations, intrauterine growth retardation, cognitive dysfunction, microcephaly, and infant mortality.

Certain general treatment paradigms to improve both maternal and fetal outcomes are commonly accepted, although many of the assumptions on which the paradigms are based are backed up by little objective evidence. Treatment standards include maintaining the best possible seizure control for the mother, or at a minimum, control of generalized tonic-clonic seizures (GTCSs). GTCSs can cause maternal or fetal hypoxia and acidosis; in addition, GTCSs have been associated with fetal intracranial hemorrhages, miscarriages, and stillbirths (3–6). The effects of nonconvulsive seizures on the developing fetus are not fully understood but may include fetal bradycardia and the consequences of trauma. Determining the direct effects on

the developing fetus of exposure to AEDs versus exposure to seizures obviously does not lend itself to a randomized trial. Nevertheless, most women will need to be maintained on an AED regimen during pregnancy. Selection of the best regimen for a particular patient must take into account the types of seizures and epilepsy syndrome, previous response to medications, family history of birth defects, side effects, and potential teratogenicity.

Another treatment paradigm that is generally accepted as being important is the use of supplemental folic acid before conception and during pregnancy (7). Proven benefits of supplemental folic acid, however, are based on studies of women without epilepsy in the general population (8) or women at high risk for neural tube defects, with a family history of the defects (9). Studies specifically designed to determine effects of fetal AED exposure have failed to show a protective effect against major malformations with folic acid administration (10–12). These findings could be due either to folic acid's inability to affect AED teratogenic mechanisms or, possibly, to the prescription of inadequate dosage levels of folic acid. Some more recent publications include recommendations that folic acid supplementation be administered at higher dosages of 4 mg to 5 mg per day when prescribing AEDs or, at least, when prescribing carbamazepine (CBZ) or valproate (VPA) (10,12,13).

An additional issue that must be considered when treating women with epilepsy during their reproductive years is that enzyme-inducing AEDs must be used cautiously with hormonal contraceptive medications. Given the importance of planned pregnancies, women need to be informed of the lower efficacy of hormonal contraceptives taken in conjunction with enzyme-inducing AEDs and encouraged to use backup barrier methods.

### Major Malformations

A major malformation is defined as an abnormality of an essential anatomic structure that is present at birth and interferes significantly with function or sustaining life or requires major intervention or both. The major malformations most commonly associated with AED exposure include congenital heart disease, cleft lip/palate, urogenital defects, and neural tube defects (14,15). Given that organogenesis occurs in weeks 3 to 10 of gestation, it is imperative that AED and vitamin regimens are carefully considered before pregnancy.

The necessity of minimizing the risk of major malformations in the offspring of women with epilepsy is obvious;

**TABLE 1.** Reports of major malformation rates by specific in utero exposures from various pregnancy registries and meta-analyses

Type of In Utero Exposure	Percentages of Major Malformation Rates (95% Confidence Intervals)	OR or RR (95% Confidence Intervals) for Major Malformations
No AED, general population	1.62% (38); 1.8% (44); 2.34% (28); 3.2% (16)	
No AED, women with epilepsy	0.8% (59); 1.7% (27); 3.0% (1.4–6.1%) (26); 3.1% (34)	OR, 0.99 (0.92–4.00) (60)
All AED exposures	3.1% (40); 3.8 (59); 4.5% (27); 6.0% (29); 9.0% (34)	OR, 1.86 (1.42–2.44) (37); RR, 2.2–2.5 (1.2–5.0) (32); OR, 3.26 (2.15–4.93) (60)
Polytherapy	6.5% (27); 6.6% (4.8–8.8%) (26); 8.6% (44); 10% (29); 15% (18); 15.6% (17); 18.8% (28)	OR, 5.1 (1.0–21.1) (44)
Monotherapy	2.34%* (39); 3.7% (3.0–4.6%) (26); 4.5% (44); 4.2% (27); 4.7% (29); 5% (18); 6.5% (17); 7.8% (34)	OR, 2.6 (0.8–8.3) (44)
PB	4.7% (44); 5.1% (34); 6.5% (2.1%–14.5%) (38)	OR, 2.7 (0.6–16.4) (44); RR, 4.2 (1.5–9.4) (38)
PHT	0.7% (0.02%–3.6%) (61); 3.4% (44); 9.1% (4.8–15.3%) (34)	OR, 1.9 (0.3–9.2) (44)
PRM	14.3% (34)	OR, 5.3 (34)
CBZ	2.3% (1.4–3.7%) (62); 2.3% (1.5–3.6%) (26); 3.0% (27); 4.9 (1.3–18.0) (24); 5.2% (44); 5.28% (28); 5.7% (34)	OR, 2.21 (1.44–3.39) (28); RR, 2.24 (1.1–4.56) (63); OR, 2.5 (1.0–6.0) (59); OR, 3.0 (0.6–16) (44); RR, 4.9 (1.3–18.0) (24)
VPA	5.9% (62); 6.0% (4.4%–8.1%) (26); 6.7% (40); 10.7% (39); 10.0% (27); 11.1% (34); 16.0% (11)	OR, 4.1 (1.5–11) (59); RR, 4.9 (1.6–15.0) (24); OR, 4.0 (34); RR, 5.0 (2.9–8.6) (39); OR, 2.51 (1.43–4.68) compared with CBZ monotherapy (37)
LTG	2.0% (40); 2.1% (62); 2.9% (1.4%–4.9%) (26); 2.9% (1.6–5.1%) (43)	

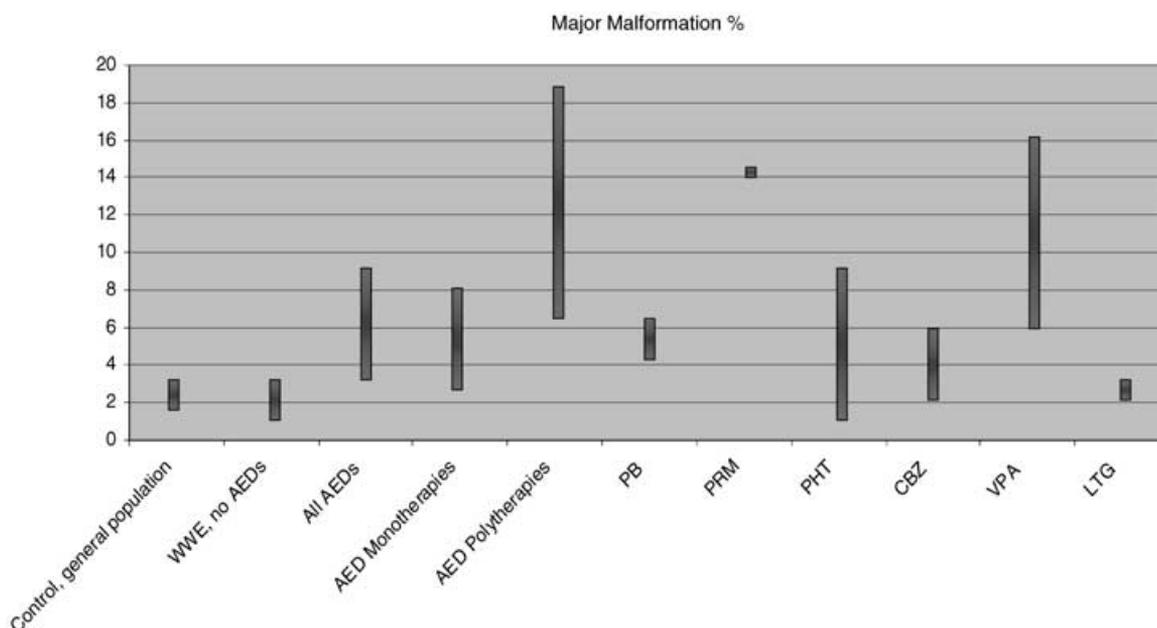
OR, odds ratio; RR, relative risk; CI, confidence interval; PB, phenobarbital; PHT, phenytoin; PRM, primidone; CBZ, carbamazepine; VPA, valproate; LTG, lamotrigine.

\*For AED monotherapies other than VPA.

therefore the primary aim of many pregnancy registries is to delineate rates of major malformations associated with different AED treatment regimens. One solidly established prescribing principle is that AED polytherapy confers a higher risk of major malformations and neurodevelopmental delay than does AED monotherapy regimens (Table 1). Sorting out differential risks between AED monotherapy regimens is more challenging. The number of patients needed to establish clearly a statistically significant difference in outcome between one AED and another is often larger than a single site can provide. Several pregnancy registries are part of multicenter studies, but, thus far, these registries have been unable to provide many solid, statistically significant conclusions. Pooling outcome data from different registries is not valid because of differences in how the information is collected and interpreted. Pregnancy registries can be based on prospective or retrospective data. The latter are fraught with selection bias, with a much higher tendency toward reports

of unfavorable outcomes. The registries differ in how major malformations are defined, up to what age identification of major malformations may be included (birth to 1 year), and whether findings of spontaneous, elective, or therapeutic abortions are included.

Use of different AED regimens during pregnancy cannot be explored with randomized, controlled trials (class I evidence), and most existing reports do not even meet class II evidence criteria. Thus prescribing physicians are forced to consider the best available evidence from ongoing observational studies in making treatment decisions. Many of the findings presented in Table 1 and in the graph that appears in Fig. 1 are preliminary and may not be statistically significant. Prospective monotherapy exposures were preferentially included in Table 1. Some of the more substantial findings are discussed in detail in the following sections. What is apparent is that consistent levels of risk are beginning to emerge from many of the pregnancy registries.



**FIGURE 1.** Reported average major malformation rates (%) by specific monotherapy exposures in utero. **WWE**, women with epilepsy; **AEDs**, antiepileptic drugs; **PB**, phenobarbital; **PRM**, primidone; **PHT**, phenytoin; **CBZ**, carbamazepine; **VPA**, valproate; **LTG**, lamotrigine.

### AED Polytherapy During Pregnancy

The reported major malformation rates in the general population vary between 1.6% and 3.2% (16), and women with a history of epilepsy who are not being administered AEDs show major malformation rates that are similar to those of the general population. The average major malformation rate among all AED exposures varies between 3.1% and 9%, or approximately twofold to threefold higher than that in the general population. Reported major malformation rates in monotherapy exposures, as a single group, are 2.3% to 7.8%, whereas AED polytherapy exposures, as a group, carry an average major malformation rate of 6.5% to 18.8%. One study of 172 deliveries, conducted in Japan, reported that the infants exposed to AED monotherapy had a malformation rate of 6.5%, whereas the infants exposed to polytherapy had a malformation rate of

15.6% ( $P = 0.01$ ) (17). A prospective study in southeast France also reported that the rate of malformations was higher in infants exposed to polytherapy (15%) than in those exposed to monotherapy (5%) ( $P < 0.01$ ) (18). The risk for major malformations is consistently higher across studies of women receiving AED polytherapy regimens, compared with women receiving AED monotherapy regimens (19–29). These findings have led to the recommendation that AED monotherapy, rather than polytherapy, be preferentially administered during pregnancy and that the conversion be achieved during the preconception planning phase (14,19).

### AED Monotherapy During Pregnancy

Although the fetal anticonvulsant syndrome has been described with virtually all of the AEDs, differential risks, once defined,

**TABLE 2.** Most commonly reported major malformations reported by specific AED exposure

Type of AED	Neural Tube Defects (NTDs)	Oral Clefts	Cardiac Malformations	Urogenital Defects (Hypospadias)
PB		+	+	
PHT		+	+	+/-
PRM		+	+	
CBZ	+		+	+
	1% (31); OR of NTDs, 6.9 (CI, 1.9–25.7) (32)			
LTG	+	+	+	+
VPA	+		+	+
	3.8% (24).			

OR, odds ratio; CI, 95% confidence interval; PB, phenobarbital; PHT, phenytoin; PRM, primidone; CBZ, carbamazepine; LTG, lamotrigine; VPA, valproate.

may facilitate improved fetal outcomes. Many reports exist for individual AED monotherapy regimens (see Tables 1 and 2). Reported major malformation rates vary among phenobarbital (PB), 4.7% to 6.5%; phenytoin (PHT), 0.7 to 9.1%; CBZ, 2.3% to 5.7%; and lamotrigine (LTG), 2.0% to 2.9%. The overall major malformation rate for VPA of 5.9% to 16.0% is conspicuously higher than that of the other monotherapy regimens.

Differences in the likelihood of specific malformations with each of the different AEDs also have been reported (see Table 2) (19). In a comparison between two cohorts, the older cohort (1972–79) included more women being administered PB, PHT, or primidone (PRM) and had higher rates of congenital heart defects, facial clefts, developmental retardation, and minor anomalies (22). The newer cohort (1981–85) comprised more patients receiving monotherapy with valproic acid (VPA) or CBZ, and the malformations identified most frequently were neural tube defects and glandular hypospadias. Arpino et al. (30) reported findings from an international database for surveillance of infants with malformations. Of the 299 cases of major malformations with first-trimester AED exposure, associations were found for spina bifida with VPA; for oral clefts with PB and methylphenobarbital (MPB); for cardiac malformations with PB, MPB, VPA, and CBZ; and for hypospadias with VPA.

A recent review pooled data from prospective studies that reported outcomes of in utero exposure to CBZ (28). Among 795 children exposed to CBZ monotherapy, 5.28% were described as having major congenital anomalies compared with 2.34% of 3,756 control children [ $P < 0.01$ ; odds ratio (OR) = 2.21; 95% confidence interval (CI), 1.44–3.39]. The major malformations most commonly reported were cardiovascular and urinary tract anomalies, cleft palate, and neural tube defects. Other studies have reported that 1% of CBZ-exposed infants had spina bifida (31) and that the adjusted OR of neural tube defects is as high as 6.9 (95% CI, 1.9–25.7) (32).

The relative risk (RR) for neural tube defects with VPA is remarkably high compared with the risk of 0.06% in the general population. One report, which pooled data from five prospective studies, suggested that the absolute risk with VPA monotherapy may be as high as 3.8% for neural tube defects and that offspring of women receiving  $> 1,000$  mg/day of VPA are especially at an increased risk (24). Other collaborative studies have supported a significant dose–response relation for VPA (11,25,33–36). Furthermore, a recent study directly compared the teratogenic effects of VPA and CBZ in monotherapy and found that exposure to VPA monotherapy, compared with CBZ monotherapy, resulted in an OR of 2.51 (95% CI, 1.43–4.68) for a diagnosis of malformations (37).

The North American AED Pregnancy Registry adheres to relatively rigid criteria for release of findings. It uses only prospective enrollees, with identification of major malformations up to five days of life. Results have been released for only

two medications thus far, PB and VPA. Of 77 women receiving PB monotherapy, five of the infants had confirmed major malformations (6.5%; 95% CI, 2.1%–14.5%). When compared with the background rate for major malformations in this hospital-based pregnancy registry (1.62%), the RR was 4.2, with a 95% CI of 1.5–9.4 (38). Outcomes from 149 VPA monotherapy exposures have been analyzed. Major birth defects occurred in 10.7% of infants, as compared with 2.8% in infants exposed to other AED monotherapies and 1.6% in external control infants (RR, 5.0; 95% CI, 2.9–8.6) (39).

In a multicenter, prospective study of pregnant women with epilepsy in Denmark, the overall major malformation rate was 3.1%; the LTG major malformation rate was 2.0%; and the VPA major malformation rate was much higher at 6.7% (40). Although the numbers of patients in several of these smaller reports are too small to draw statistically significant conclusions, a consistent pattern is emerging among several of these studies (41). In 1998, the American Academy of Neurology published the *Practice parameter: management issues for women with epilepsy (summary statement)*, which proposed, as a guideline, that the AED selected should be the one deemed most appropriate for seizure type, with monotherapy as the aim of treatment. More recently published guidelines from the United Kingdom, the National Institute for Clinical Excellence (NICE) guidelines, advise specific caution in the use of VPA in women considering pregnancy (42).

## Newer AEDs

The newest generation of AEDs consists of a large number of structurally diverse compounds, most of which have demonstrated teratogenic effects in preclinical animal experiments. With the possible exception of LTG, none of the agents has been sufficiently tested during human pregnancy to assess safety or teratogenicity. Preliminary reports of experience with these agents during pregnancy are provided in Table 3, but prospective population-based studies in postmarketing evaluation with larger numbers of patients are essential to establish safety in human pregnancies.

The most recent results from the LTG pregnancy registry are based on 414 first-trimester monotherapy exposures (43). The major malformations rate was 2.9% (95% CI, 1.6–5.1%). Reported birth defects included all common AED categories and were not of a consistent pattern. Although the sample size is still insufficient to reach definitive conclusions about the possible teratogenic risk of LTG, the results are encouraging for LTG monotherapy.

## Neurodevelopmental Outcome

The majority of studies investigating cognitive outcome in children of women with epilepsy report an increased risk of mental deficiency, affecting 1.4% to 6% of children of women with

**TABLE 3.** Preliminary reports of major malformation rates for the newer AEDs

Type of AED	Malformation Rates
LTG	2.0% (40); 2.1% (62); 2.9% (1.4–4.9%) (26); 2.9% (1.6–5.1%) (43)
GBP	0/11 on monotherapy 6% (2/33) polytherapy (65)
LEV	0/3 on monotherapy (66)
OXC	0/35 on monotherapy; 5% (1/20) polytherapy (67); 5% [2/37 (1 major malformation was on monotherapy and 1 on polytherapy)] (40); 11% (1/9) monotherapy (59); 0 (0/101) monotherapy (27)
ZNS	7.7% [2/26, (both major malformations were on polytherapy)] (68)
TPM	0/19 monotherapy cases; 24.2% (8/33) polytherapy (69)

GBP, gabapentin; LEV, levetiracetam; OXC, oxcarbazepine; ZNS, zonisamide; TPM, topiramate.

epilepsy, compared with 1% of controls (3,45,46). Verbal scores on neuropsychometric measures may be selectively more involved than nonverbal tasks (20,47,48). A variety of factors contribute to the cognitive problems of children of mothers with epilepsy, but AEDs appear to play a role (48). Studies on particular AEDs (Table 4) indicate that the child's level of IQ is negatively correlated with in utero exposure to PRM (47), PB (49), PHT (20,50), CBZ (20,28,51), VPA (20,52), and polytherapy (20,47,52,53). A recent study reported significantly reduced verbal IQ scores in the polytherapy group ( $n = 30$ ) and in the VPA monotherapy group ( $n = 13$ ), but the CBZ group ( $n = 86$ ) demonstrated no differences from controls (54). Another recent retrospective study of 249 children ages 6 and over demonstrated a significantly lower mean verbal IQ in the valproate group compared to other monotherapy groups and the unexposed group. Multiple regression analysis demonstrated that in addition to valproate exposure, lower maternal IQ and five or more tonic-clonic seizures during pregnancy were independently predictive of lower verbal IQ (55).

Exposure to seizure medicines during the last trimester may actually be the most detrimental (49). Other factors, associated with cognitive impairment include a high number of minor anomalies, major malformations, decreased maternal education, impaired maternal-child relations, and maternal partial seizure disorder (56). It is possible that these risk factors are not only additive but also potentially synergistic. Microcephaly has been associated with in utero AED exposure (3,57), especially for polytherapy, PB, and PRM (58).

## Conclusion

Although women with epilepsy do have increased risks for maternal and fetal complications, these risks can be consid-

**TABLE 4.** Reports of neurodevelopmental delay by specific in utero AED exposures

In Utero Exposure	Neurodevelopmental Delay
No AED, general population	1% (3,45,46)
All AED exposures	1.4–6% (3,45,46) OR for AEN, 1.49 (CI, 0.83–2.67) (52) + (20,47,52)
Polytherapy	Verbal IQ mean, 85 (CI, 80–90) (54); Reduced verbal IQ scores in the polytherapy group (54); 4/7 studies demonstrated poorer developmental outcome in with polytherapy in utero compared with monotherapy regimens (53); OR for AEN, 2.51 (CI, 1.04–6.07) (52) OR for AEN, 1.27 (CI, 0.66–2.45) (52) + (49)
Monotherapy	
PB	+ (20,50)
PHT	+ (47)
PRM	+ (20,28,51)
CBZ	No difference from controls (54) + (20,55)
VPA	Lower verbal IQ, 82 (CI, 78–87) (54); OR for AEN, 3.4 (CI, 1.63–7.10) (VPA monotherapy) (52)

OR, odds ratio; AEN, additional educational needs; CI, 95% confidence interval; PB, phenobarbital; PHT, phenytoin; PRM, primidone; CBZ, carbamazepine; VPA, valproate.

erably reduced with careful selection of AED treatment regimens. Prescribing AEDs for women during their reproductive years should include the constant consideration of pregnancy, planned or unplanned. Treatment paradigms that are generally accepted include use of monotherapy (at the lowest effective dose for seizure control) and folic acid supplementation. Over time, the reported major malformation rates have declined in offspring of women with epilepsy, as the percentage of women receiving polytherapy has decreased. Fetal outcomes may be improved further with clarification of differential risks for the various AED monotherapy regimens. In the absence of class I evidence, clinicians must select AEDs by using information that is currently available from observational studies, with constant reassessment as new findings are reported.

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