Teratogenic Effects of Antiepileptic Medications

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KEYWORDS

• Epilepsy • Pregnancy • Antiepileptic drugs
• Teratogenicity • Birth defects

It has been estimated that 0.3% to 0.5% of all children are born to mothers with epilepsy,[1,2] corresponding to approximately 25 000 children each year in the United States alone.[3] With increasing use of antiepileptic drugs (AEDs) for other indications, such as psychiatric conditions, migraines, and pain disorders, the number of women using AEDs during pregnancy is likely to be considerably higher. Although the focus of this article is on the potential teratogenic effects of AEDs, it is important to underline that the potential adverse outcomes in the offspring because of maternal use of AEDs need to be weighed and balanced against the risks associated with the underlying disease itself. In epilepsy, the maternal and fetal risks with uncontrolled major convulsive seizures generally necessitate continued drug treatment during pregnancy.[4] The challenge to physicians is to prescribe a treatment that effectively controls generalized tonic-clonic seizures in particular while minimizing the risk of adverse AED effects on the fetus. This is a realistic goal because most women with epilepsy have uneventful pregnancies and give birth to perfectly normal children.

The first report suggesting an association between use of AEDs and major congenital malformations was published more than 40 years ago.[5] This short report described oral clefts and some other abnormalities in 6 children who were exposed to phenytoin, phenobarbital, and primidone in different combinations.[5] Subsequent studies during the following decade, mainly retrospective case series, confirmed that use of all the major older generation AEDs, such as phenobarbital, phenytoin, valproate, and carbamazepine, was associated with an increased risk of birth defects.[6] Later, prospective cohort studies tried to distinguish between the contributions of AEDs versus the underlying epilepsy to the adverse fetal outcome, and case-control studies analyzed specific birth defects in relation to individual AEDs. The last decade has seen the

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establishment of epilepsy and pregnancy registries. These prospective observational studies aim at enrollment of large numbers of pregnant women with the ultimate goal of comparing the teratogenic potential of different AEDs.[7] These data are reviewed in this article with emphasis on findings that have emerged during the last 5 to 10 years.

SOME METHODOLOGIC ASPECTS

The methodologies that have been applied vary with the specific objectives of the studies. Case-control designs are useful for uncommon outcomes and have been used to analyze the association between specific types of malformations and exposure to AEDs. The risk of recall bias is a problem shared by case-control and other types of retrospective studies. A woman with unfavorable outcome of her pregnancy is more likely to remember various exposures during pregnancy than a woman with a normal pregnancy outcome. A prospective design with enrollment in the study and recording of exposure before pregnancy outcome is known is important to avoid recall and selection bias. With the more widespread use of early prenatal diagnostic tests, it is becoming increasingly difficult to enroll purely prospective pregnancies.

It must be kept in mind that even properly conducted prospective clinical studies of teratogenic outcomes are observational. For ethical and practical reasons, no randomized controlled trials compare the teratogenicity of different AEDs. Women have not been allocated to their AED, dosage, and dosage schedule by chance but rather based on various individual characteristics, including seizure type and epilepsy classification, educational level, other socioeconomic circumstances, comorbidities, and family history of birth defects. Some of these factors that contribute to the AED selection also might affect pregnancy outcome. An association between a particular drug and high malformation prevalence does not necessarily mean a causal relationship. Observational studies need to consider these potential confounding factors, obtain such information, and try to control for those in the analyses.

An additional concern relates to the generalizability of the observations. There is a spectrum of different methods used to enroll pregnant women. Each method affects differently the representativeness of the cohort. This must be kept in mind when study results are interpreted and translated into general treatment recommendations. Until recently, most cohort studies recruited patients from single or a few collaborating epilepsy centers, thus generally selecting more severe cases. For obvious reasons, the cohorts were small, each rarely exceeding 500 pregnancies.[6,8] They were not powered to analyze specific types of malformations, compare different AEDs, or to include important confounding factors in their analyses. Because of these shortcomings, pregnancy registries have been designed to prospectively enroll larger cohorts of pregnant women and enable more refined analyses of teratogenic effects. Some registries are not specifically established for assessment of AEDs but have been used for that purpose. Examples are national drug prescription databases that are cross-linked with registries of birth defects.[9,10] Such registries may have the advantage of being population-based and sometimes nationwide and representative. They generally lack information on other factors that could contribute to the outcome, however, including the indication for treatment drug dosage.

Specific AED and pregnancy registries have been operational for approximately 10 years. Some are organized by pharmaceutical companies and only collect data on the manufacturers' own product, which makes the results difficult to interpret in the absence of a comparator.[11] Others are organized by independent research groups and include information on all AED exposures.[7] They may be regional (eg, Australia, United Kingdom, North America) or international (European and International Registry

of Antiepileptic Drugs in Pregnancy, EURAP). Using slightly different methodologies, each of these groups has been successful in enrolling thousands of pregnancies with AED exposure. Each group records the type of drug exposure in an unbiased way without prior knowledge of teratogenic outcome, and detailed data on other relevant patient characteristics are obtained. The internal validity of the risk assessments is likely to be high, whereas the possibility to generalize from the results depends on how pregnancies were enrolled. Many of these registries have released results that are discussed later.

The pregnancy registries focus on major congenital malformations—or birth defects—as teratogenic outcome. Other types of cohort studies have assessed possible adverse effects of AED exposure in utero on postnatal cognitive development. Sample sizes are considerably smaller, but because they also are observational, controlling for confounding factors remains an important issue.

MAJOR CONGENITAL MALFORMATIONS

Epilepsy or Antiepileptic Drugs

The prevalence of major congenital malformations in offspring of women with epilepsy has ranged from 4% to 10%, corresponding to a 2- to 4-fold increase from the expected prevalence in the general population.[4,7,12] Available data strongly suggest that this risk increase is caused mainly by AED exposure rather than epilepsy or seizures. Pooled data from 26 studies, including outcomes in treated and untreated women with epilepsy and healthy women, revealed a malformation rate of 6.1% in offspring of women with epilepsy who were treated with AEDs, 2.8% among children of women with untreated epilepsy, and 2.2% in the healthy control group.[12] These observations are in line with a meta-analysis based on 10 studies reporting rates of congenital malformations in offspring of untreated women with epilepsy.[13] The malformation rate in this group was not higher than among offspring of healthy controls without epilepsy (odds ratio [OR] 1.92; 95% CI 0.92–4.00). Although untreated women with epilepsy are different in many respects from women who are under treatment during pregnancy, these data convincingly demonstrate that treatment is the major cause of increased risks of birth defects, although epilepsy-related factors should not be totally disregarded.

Polytherapy with AEDs is associated with a higher malformation rate (6.8%) than monotherapy (4%) in a pooled analysis.[12] This has been a consistent finding throughout most studies. Although alternative interpretations are possible because of confounding factors, this observation provides supportive evidence for the contribution of drug treatment to the increased risk of birth defects in children of women with epilepsy. It should be acknowledged that these conclusions are based mainly on studies reflecting the use of AEDs 10 to 25 years ago, when drug selection, dosing, treatment strategies, and monitoring were different compared with today.

Patterns of Malformations

The pattern of malformations in children born to women with epilepsy is mostly the same as seen in the general population, with cardiac defects being the most common followed by facial clefts and hypospadia.[8] The pattern may vary with the type of AED, however. Neural tube defects and hypospadias are more common among offspring of mothers who used valproate during pregnancy; the risk of neural tube defects in association with use of valproate has been estimated at 1% to 2%.[14] An increased risk of neural tube defects of 0.5% to 1% has been reported after carbamazepine exposure.[15,16] Recent data from the North American AED Pregnancy Registry suggested

a 10-fold increase in risk of oral clefts among lamotrigine-exposed infants,[17] but this specific association has not been confirmed in other registries.[17,18]

Comparative Teratogenic Potential

For the woman with epilepsy who needs treatment and for her physician, the important question is whether AEDs differ in their teratogenic potential. Malformation rates reported from pregnancy registries for the 5 most frequently used AEDs (valproate, carbamazepine, lamotrigine, phenobarbital, and phenytoin) are summarized in **Table 1**.

GlaxoSmithKline's International Lamotrigine Pregnancy Registry[11] reported a malformation rate of 2.9% based on 802 monotherapy exposures, which is difficult to interpret in the absence of a comparator. The Finnish drug prescription database is a population-based nationwide registry. It has been cross-linked with the National Medical Birth Registry to identify 1411 pregnancies with AED exposure.[9] The risk of malformations was higher in children exposed to valproate monotherapy than in untreated patients (malformation rate 10.6%; OR = 4.18; 2.31–7.57). In contrast, the risk of malformations was not elevated in association with exposure to carbamazepine, oxcarbazepine, or phenytoin monotherapy. Another population-based nationwide registry, the Swedish Medical Birth Registry, reported 1398 pregnancies with exposure to AEDs.[10] The risk for severe malformations in offspring was greater after exposure to valproate compared with carbamazepine monotherapy (OR = 2.59; 95% CI: 1.43–4.68).[9] Updated malformation rates for the 4 most frequently used AEDs in this registry are provided in **Table 1**.[19]

The largest AED and pregnancy registries are The North American Antiepileptic Drugs and Pregnancy Registry (NAAPR), the United Kingdom Epilepsy and Pregnancy Register, and EURAP, an international registry enrolling pregnancies from more than 40 countries, in Europe, Australia, Asia, Oceania, and South America.[7] These registries have enrolled 6000 to 13 000 pregnancies; 2 of them—NAAPR and the UK register—have published results on teratogenic outcome. NAAPR initially disclosed malformation rates associated with specific treatments when found to differ significantly from the background rate. Increased malformation rates in comparison with the general population have so far been identified with phenobarbital (relative risk [RR] 4.2; 95% CI 1.5–9.4)[20] with a malformation rate of 6.5% based on 77 monotherapy exposures and valproate (RR 7.3; 95% CI 4.4–12.2),[21] malformation rate 10.7% (149 exposed). Subsequently, and based on new criteria, NAAPR reported malformation rates of

Table 1
Malformation rates and percentage (number of exposures) with different antiepileptic drugs in monotherapy in different registries

Registry	Valproate	Carbamazepine	Lamotrigine	Phenobarbital	Phenytoin
GlaxoSmithKline[11]	—	—	2.9% (802)	—	—
Finnish Drug prescription[9]	10.6% (263)	2.7% (805)	—	—	—
Swedish Medical Birth Registry[19]	7.7% (507)	5.4% (1199)	4.9% (400)	—	7.6% (145)
UK Register[24]	6.2% (715)	2.2% (900)	3.2% (647)	—	3.7% (82)
North American Registry[17,20–23]	10.7% (149)	2.5% (873)	2.8% (684)	6.5% (77)	2.6% (390)
Australian Register[25]	13.3% (166)	3.0% (234)	1.4% (146)	—	3.2% (31)

2.8% (n = 684) with lamotrigine monotherapy,[17] 2.5% (n = 873) with carbamazepine,[22] and 2.6% (n = 390) with phenytoin monotherapy.[23]

The UK register published their first report based on 3607 cases.[24] The rate of major congenital malformations for pregnancies exposed to valproate monotherapy was 6.2% (4.6%–8.2%) compared with 2.2% (1.4%–3.4%) for carbamazepine. The malformation rate with lamotrigine monotherapy was 3.2% (2.1%–4.9%) based on 647 pregnancies. Interestingly, the malformation rate in offspring of 227 untreated women with epilepsy was 3.5% (1.8%–6.8%), which was similar to the 3.7% rate (3.0%–4.5%) among the pregnancies with monotherapy exposure in general (n = 2468). **Table 1** indicates that malformation rates across studies vary considerably for the same AED in monotherapy. Carbamazepine exposure was associated with rates ranging from 2.2% to 5.4%, lamotrigine had rates from 1.4% to 4.9%, phenytoin from 2.6% to 7.6 %, and valproate had rates ranging from 6.2% to 13.3% (**Table 1**). The wide ranges in malformation rates reflect differences in study populations, criteria, and methodology. Prevalences of malformations with different AEDs should not be compared across studies. There seems to be a consistent pattern within studies with higher rates with valproate and lower rates with carbamazepine and lamotrigine, however (**Table 1**). Even within-study comparisons should be made with caution considering the possible effects of confounding factors.

Data on pregnancy outcomes with other new generation AEDs than lamotrigine are still scarce. Reports on malformation rates in prospective pregnancies with monotherapy exposure to gabapentin, topiramate, levetiracetam, oxcarbazepine, and zonisamide are summarized in **Table 2**. The table is based on data from peer-reviewed publications with an exception made for the latest release from NAAPR, so far available only as abstract.[9,19,23–37] Even when pregnancies from several different studies are added up, the total number of monotherapy exposures for each of gabapentin, topiramate, levetiracetam, and oxcarbazepine ranges are approximately 240 up to

Table 2
Monotherapy exposures and number with major malformations with some newer generation antiepileptic drugs

Reference	Gabapentin	Topiramate	Levetiracetam	Oxcarbazepine	Zonisamide
Kondo et al.[26]	—	—	—	—	4 (0)
Samrén et al.[27]	—	—	—	2 (0)	—
Fonager et al.[28]	1 (0)	—	—	14 (0)	—
Hvas et al.[29]	—	—	—	7 (0)	—
Long[30]	—	—	3 (0)	—	—
Montouris[31]	16 (1)	—	—	—	—
Kaaja et al.[32]	—	—	—	9 (1)	—
Meischenguiser et al.[33]	—	—	—	35 (0)	—
Källen[19]	68 (5)	—	—	4 (0)	—
Artama et al.[9]	—	—	—	99 (1)	—
UK registry[24,36,37]	31 (1)	42 (1)	39 (0)	—	—
Ornoy et al.[34]	—	29 (1)	—	—	—
ten Berg et al.[35]	—	—	11 (0)	—	—
Holmes et al.[23]	127 (1)	197 (8)	197 (4)	121 (2)	
TOTAL	**243 (8)**	**268 (10)**	**250 (4)**	**291 (4)**	**4 (0)**

290. For zonisamide exposure, only four pregnancies were reported. Clearly these numbers are too small for a reliable assessment of the risks.

EFFECTS ON POSTNATAL COGNITIVE DEVELOPMENT

In 2004, a Cochrane Review concluded that most studies on developmental effects of AEDs are of limited quality and that there was little evidence about which drugs carry more risks than others to the development of children exposed.[38] More recently, some studies suggested that exposure to valproate might be associated with a risk of adverse cognitive development.[39–43] A retrospective survey from the United Kingdom indicated that additional educational needs were more common among children who were exposed to valproate or carbamazepine than controls.[39] A follow-up investigation of partly the same cohort revealed significantly lower verbal IQ in children exposed to valproate monotherapy (mean 83.6; 95% CI 78.2–89.0; n = 41) than in unexposed children (90.9; 95% CI 87.2–94.6; n = 80) and children exposed to carbamazepine (94.1; 95% CI 89.6–98.5; n = 52) or phenytoin (98.5; 95% CI 90.6–106.4; n = 21).[40] Multiple regression analysis found exposure to valproate, 5 or more tonic-clonic seizures in pregnancy, and low maternal IQ to be associated with lower verbal IQ. Doses of more than 800 mg/d were associated with lower verbal IQ than lower doses, for which no differences were seen compared with other monotherapies. These results should be interpreted with caution given the small numbers, the retrospective nature of the study, and the fact that only 40% of eligible mothers agreed to participate.

Two small population-based prospective studies from Finland, each including only 13 children who were exposed to valproate in utero, reported similar trends with worse cognitive outcome compared with other exposures.[41,42] Findings were not statistically significant, however, which may be explained by the small sample size and existence of confounding factors.[42] The first reasonably powered prospective comparative study of cognitive effects of children exposed to AEDs recently published interim results of the children 3 years of age.[43] Women taking valproate, carbamazepine, lamotrigine, or phenytoin were enrolled in early pregnancy, and the cognitive development of their children was assessed at 3 years. Children exposed to valproate (n = 53) had significantly lower IQs (92; 95% CI 88%–97%) than children exposed to the other AEDs (carbamazepine 98 [n = 73]; lamotrigine 101[n = 84]; phenytoin 99 [n = 48]), whereas IQ scores did not differ significantly among children exposed to the other 3 AEDs. There was a significant correlation between the valproate dose in pregnancy and a child's IQ. In fact, children exposed to valproate doses of less than 1000 mg/d did not differ in IQ from children exposed to other AEDs.

These observations are intriguing, and the results are in line with those of previous retrospective and smaller studies. It should be noted, however, that IQs in children exposed to valproate were in the normal range. Because of the observational design, one cannot completely exclude some influence of confounding factors, such as possible differences in seizure control during and after pregnancy and breast-feeding. This is an interim analysis of a study for which the primary outcome is at 6 years.

DOSE DEPENDENCY

A dose-effect relationship has so far been shown most consistently for teratogenicity in association with valproate. Dosages of more than 800 to 1000 mg/d have been associated with significantly greater risks than lower dosages, as summarized in **Table 3.**[9,24,25,27,44,45] Data on cognitive outcome reveal a similar pattern. The retrospective study from Liverpool found that verbal IQ was no different from unexposed controls among children exposed to valproate doses of less than 800 mg/d.[40]

Table 3
Studies reporting a dose–effect relationship with malformations and valproate exposure

Reference	High Risk (mg/d)	Low Risk (mg/d)	Malformation Rate Low VPA Dose	Malformation Rate Other Monotherapy
Samrén et al[44]	>1000	<600	Not available	Not available
Samrén et al[27]	>1000	<600	Not available	Not available
Kaneko et al[45]	>1000	<1000	1.9%	7.2%
Artama et al[9]	>1500	<1500	9.5%	2.5%
Vajda et al[25]	>1100	<1100	5.4%	3.0%
Morrow et al[24]	>1000	<600	4.1%	2.7%

Likewise, the prospective NEAD study found the IQ of children whose mothers took valproate in doses less than 1000 mg/d to be similar to IQs in children exposed to other AEDs.[43] The UK Epilepsy and Pregnancy Register also reported a positive dose response for major congenital malformations for lamotrigine. Doses more than 200 mg/d were associated with higher risks.[24] This pattern was not found in the International Lamotrigine Registry of GlaxoSmithKline, however, and the North American pregnancy registry did not find lamotrigine doses to be significantly higher in mothers of children with malformations compared with mothers of healthy children.[11]

SUMMARY

Data on clinical teratogenicity are at best derived from carefully conducted observational studies, whereas randomized, controlled trials have no place in this research area. We can only expect level B recommendations and lower. New relevant information has become available during the last 5 years on pregnancy outcomes with 3 of the most frequently used AEDs: carbamazepine, valproate, and lamotrigine. It seems that birth defect rates with carbamazepine monotherapy are lower than previously thought. In some large studies rates are only marginally increased compared with different control populations. More recent data do not suggest adverse effects of carbamazepine on cognitive development.

The overall prevalence of malformations in association with lamotrigine exposure seems to be similar to that of carbamazepine. The only available prospective study on cognition does not indicate any adverse effects of lamotrigine.[43] Malformation rates with valproate have consistently been found to be 2 to 3 times higher compared with carbamazepine or lamotrigine. More limited data also suggest adverse effects of high doses of valproate on cognitive development of the exposed child. For newer generation AEDs other than lamotrigine, data are still too limited to determine the risks for birth defects and are nonexisting with respect to possible adverse effects on cognitive development. Doses are important, and evidence is lacking for higher risks with valproate compared with other AEDs if doses are less than 800 to 1000 mg/d. Confounding factors contribute to some of the apparent differences between AEDs in pregnancy outcomes, and more data are needed, particularly concerning cognitive outcomes and specific birth defects.

Based on these observations, valproate should not be a first-line AED for women who are considering pregnancy. In this situation this drug is best avoided if other effective but safer AEDs can be found for each individual woman's seizure disorder. Based on pregnancy outcome data, carbamazepine seems comparatively safe and a reasonable first-line choice in localization-related epilepsy. Alternatives are less clear in

idiopathic generalized epilepsies. Lamotrigine seems comparatively safe, but its use in pregnancy is complicated by pharmacokinetic changes and risks of breakthrough seizures.[46] The experience with use of levetiracetam and topiramate during pregnancy is still insufficient.

Any attempt to change drugs should be completed and evaluated before conception; withdrawals or other major changes should be avoided during pregnancy. These conclusions are largely in line with the recently published report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society.[47]

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