

Neurological teratogenic effects of antiepileptic drugs during pregnancy (Review)

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Abstract. Epilepsy is one of the few neurologic disorders that requires a constant treatment during pregnancy. Epilepsy affects 0.3-0.8% of pregnant women. Prescription of anti-epileptic drugs (AEDs) to pregnant women with epilepsy requires monitoring and maintaining a balance between limiting seizures and decreasing fetal exposure to the potential teratogenic effects. AEDs are also commonly used for psychiatric disorders, pain disorders, and migraines. The types of malformations that can result in fetuses exposed to AEDs include minor anomalies, major congenital malformations, intrauterine growth retardation, cognitive dysfunction, low IQ, microcephaly, and infant mortality. In the present review, we analyzed and summarized the current understanding of neurological development in fetuses that are exposed to various AEDs administered to pregnant epileptic women.

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1. Introduction

In the United States, mothers with epilepsy give birth to more than 30,000 children/year. Antiepileptic drugs (AEDs) are a class of drugs that are used to treat epilepsy in patients. AEDs are administered to most epileptic patients, including pregnant women; however, they can have negative consequence to fetuses *in utero* (1). AEDs are also used to treat other diseases as well such as neuropathic pain, migraines and psychiatric disorders, which means that AEDs can affect other pregnancies as well (2). Therefore, many pregnant women are being exposed to the potential dangerous effects of AEDs to the fetuses. However, AEDs are important for the treatment of epilepsy in pregnant mothers. Most women with epilepsy require AEDs to control seizures the entire length of the pregnancy. The most concerning issue in pregnant women with epilepsy is the development of tonic-clonic seizures, which can lead to dangerous issues for the fetus such as intracranial hemorrhage, transient hemorrhage and heart beat abnormalities (3,4).

There may be multiple mechanisms through which AEDs affect fetal neurodevelopment. While scientists have still not properly characterized the pathways through which this may occur, a number of studies have investigated the mechanism through which this may occur. Cognitive defects can still occur in fetuses that are exposed to AED dosages that are lower than those that produce structural abnormalities. There are various hypothesis that have been set forward that may explain the ability of AEDs to produce functional defects; these may include suppression of neurons, ischemic condition *in utero*, formation of free radicals, apoptosis in neurons and decreased folate metabolism (Fig. 1) (5).

2. AED induced birth defects

The statistics for pregnant women taking AEDs are morbid, as 30% of pregnancies result in maternal mortality and 50% result in fetus mortality (6). Despite these odds, the majority of doctors encourage the use of AEDs during pregnancy. This is because, generally, women with epilepsy have normal childbirths and the offspring are born without any structural abnormalities. However, compared to a normal pregnancy, there is still a higher chance of the children to be born with birth defects (4).

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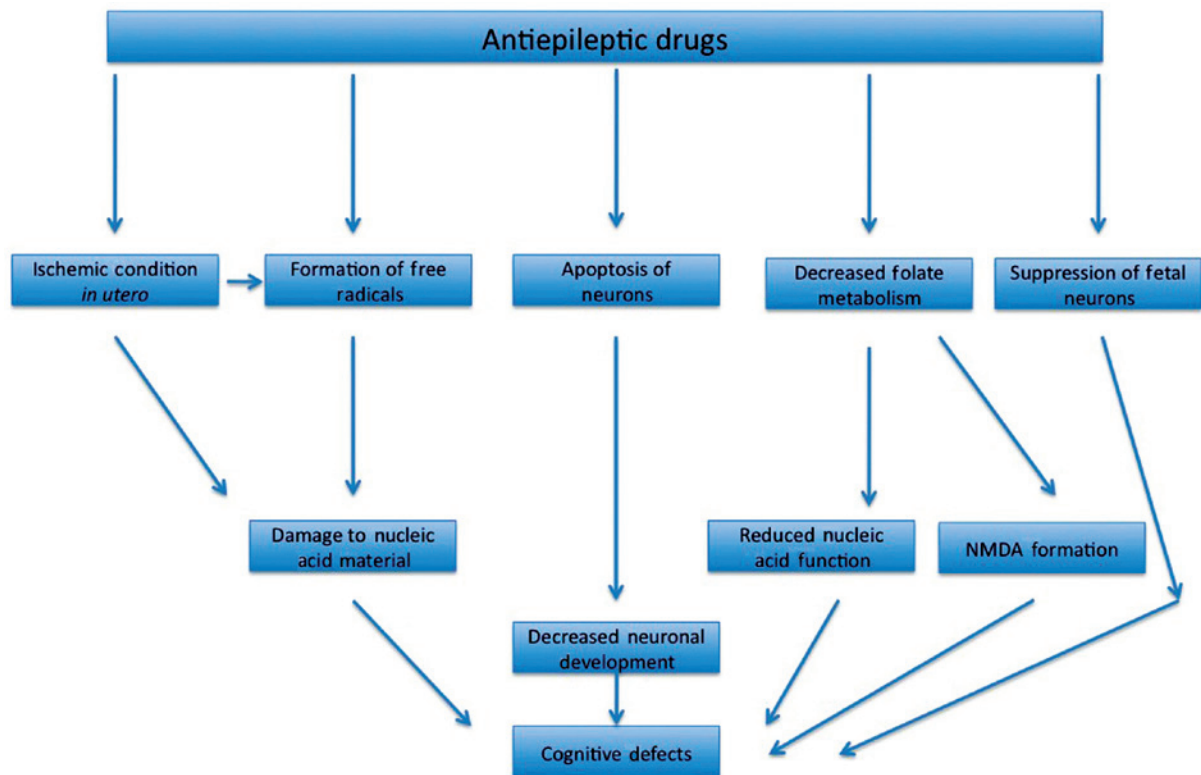


Figure 1. Various hypotheses that explain the teratogenicity of AEDs. There may be multiple mechanisms that lead to the formation of cognitive defects in fetuses, including ischemic condition, neural suppression, decreased folate absorption, neural apoptosis and an increase in free radical formation (5). AEDs, antiepileptic drugs.

A meta-analysis found that pregnant women with epilepsy that are on AEDs have a 6.1% chance of the development of major congenital malformations (7). Different AEDs have a different major congenital malformation rate (Fig. 1). Women with epilepsy that are not on AEDs have a 2.8% rate of major congenital malformation, which is slightly higher than the control group at 2.2% (8). When only treated with one AED (AED monotherapy), the prevalence of major congenital malformations is 3.7% while it is 6% in pregnant women that are treated with AED polytherapy. The types of malformations that are observed due to AED exposure *in utero* include cardiac malformations, hypospadias and facial clefts (9). The potential effects of some AEDs have been well-established but the effects of others remain unclear. One particular example of a specific malformation is the use of the drug valproate, which causes a 1-2% risk of neural tube defects (10) (Table I).

3. Neurobehavioral endpoints with AEDs

Evidence from a variety of studies has shown that there is a definite correlation between the *in utero* exposure to various AEDs and the risk of cognitive and behavioral problems in children (6,11). The Kerala Registry of Epilepsy and Pregnancy conducted a study and determined that children that were exposed to AEDs *in utero* had the lowest mental development scores when compared to healthy controls (12). The mental development scores were found to be the lowest in children that were exposed to valproic acid. The mental development scores in children exposed to valproic acid were decreased by 40.8% when compared to controls. Other AEDs

Table I. Major congenital malformation rate due to *in utero* exposure to various AEDs.

Antiepileptic drug	MCM rate (%)
Carbamazepine	2.20
Valproic acid	6.20
Lamotrigine	3.20
Phenytoin	3.70
Gabapentin	3.20
Topiramate	7.10

These AEDs include carbamazepine, valproic acid, lamotrigine, phenytoin, gabapentin and topiramate (7). AEDs, antiepileptic drugs.

such as phenytoin, carbamazepine and phenobarbital also led to decreased mental development scores by 37, 29 and 26%, respectively (12).

Another study conducted by Meador *et al* demonstrated that at the age of 3, children that were exposed to the AED valproic acid *in utero* had the lowest IQ score. The mean IQ score for fetuses exposed to valproic acid was 92, which was 7 and 9 points lower, respectively, than the children that were exposed to carbamazepine and lamotrigine (5). In fact, the IQ of the offspring correlated with the mother's IQ in every case except for the exposure to valproic acid. Thirteen percent of children that were exposed *in utero* to valproic acid presented

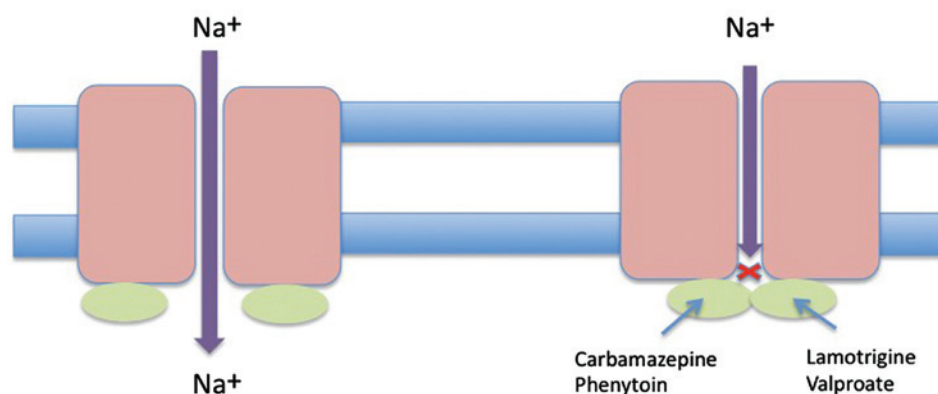


Figure 2. Mechanism of AEDs. Carbamazepine, phenytoin, lamotrigine and valproate work by inactivating voltage-gated sodium channels (18). AEDs, anti-epileptic drugs.

with IQs that were in the impaired range; this is contrasted to 5% of children that were exposed to phenytoin, 3% of children that were exposed to carbamazepine and 2% of children that were exposed to lamotrigine (5,13). Another study tested the ability of children exposed *in utero* to AEDs to generate quantity and quality of ideas. The study showed that both the quantity and quality of ideas were lower in children that were exposed to valproic acid when compared to the children that were exposed to lamotrigine and carbamazepine. Even in studies done in older children, AED *in utero* exposure was found to lead to altered cognitive function (14). Gaily *et al* found that older children that were exposed to monotherapy *in utero* had decreased performance on attentional tasks while being exposed to polytherapy led to decreased performance in auditory attention, sentence repetition and fine motor task (15). Long-term studies have shown that all AEDs, except for carbamazepine, led to a negative result in terms of intellectual function (16).

4. Effects of different AEDs on neural defects

There are various AEDs that have been investigated due to their potential for teratogenicity in pregnant women. Due to the fact that AEDs should not be discontinued during pregnancy, this is an issue that needs to be elaborated on extensively. The AEDs that we discuss in this review are phenobarbital, valproate, carbamazepine, lamotrigine, phenytoin and topiramate. The mechanism by which these drugs impart their action is by inhibiting the voltage-gated sodium channel (Fig. 2) (17).

5. Phenobarbital

Phenobarbital is one of the oldest AEDs that have been used to treat epilepsy in all patient cohorts. The effect of phenobarbital on fetuses was not evaluated until the 1970s. A study performed on pregnant mice using phenobarbital suggests that it leads to a 4.3% increase in incidences of cleft palates in fetuses (18). Phenobarbital exposure to pregnant rats has also led to an increased incidence of fetus mortality, impaired growth and delayed motor development. The mechanism behind phenobarbital-induced neural issues in the fetus may be related to the upregulation of cytochrome P450s of the 2B family. It may act to produce oxidative stress by generating

superoxide radicals, which leads to the production of hydroxyl radicals. This causes GC to TA transversions, which may eventually lead to developmental defects (19,20).

6. Valproic acid

Valproic acid and its various analogs and metabolites have been researched regarding their ability to assert a teratogenic effect. In order to be teratogenic, the drug needs to have the following components: A free carboxyl group, an α -hydrogen atom, branching of carbon chains, no double bonds on C-2 or C-3 and an alkyl substituent on the C-2 that is larger than the methyl groups (21). Valproic acid and its effects have been analyzed across various animal systems such as zebrafish, mouse, rat, hamster and others (22-26). When valproic acid is administered at high enough dosages, such as those between 200-800 mg/day in mice, valproic acid induces various developmental defects, such as skeletal defects in craniofacial bones, in a dose-dependent manner. Increased doses of valproic acid were also found to lead to intra-uterine growth retardation, craniofacial, skeletal and cardiac defects (27).

In addition, rodents that were exposed to valproic acid were found to have fetuses that presented with neural tube defects. Valproic acid administration, when administered during early neural tube formation, can lead to exencephaly. Neural tube defects were found to be caused by $>225 \mu\text{g/ml}$ of valproic acid, which is above the concentration recommended for humans. The mechanism of the neural tube defect induced by valproic acid may be a result of altered folate metabolism in the embryo by increasing the tetrahydrofolate levels and decreasing levels of 5-formyl- and 10-formyltetrahydrofolates (28).

7. Carbamazepine

Carbamazepine, which is used as treatment for epilepsy and bipolar disorder, has been reported to lead to congenital abnormalities when used during pregnancies. Many articles have reviewed the first trimester exposure to carbamazepine and found that there was an increase in malformations such as neural tube defects, developmental delays, craniofacial defects and behavioral changes (29). A study by Diav-Citrin *et al* found that a cohort of pregnant women treated with carbamazepine showed a lack of neural tube defects, though that may

be due to sample size limitation (30). Another study showed that offspring of epileptic pregnant women that were treated with carbamazepine led to a 10-mm decrease in fetal head circumference, which did not become normal by the age of 18 months (31). Other studies have also found that carbamazepine exposure *in utero* has led to craniofacial defects and developmental delays. Therefore, carbamazepine is considered a human teratogen as it leads to major and minor abnormalities in fetuses and babies such as developmental problems, abnormal IQ and growth retardation (32).

8. Lamotrigine

Lamotrigine is one the newer AEDs and therefore, there is not much long-term information available on its effect on fetus development. GlaxoSmithKline (London, UK) began a database of women on lamotrigine in 1992, which is where much of the current data on this drug originates. The database recognized that women on lamotrigine presented with fetal malformations at a rate of 2.7% when compared to the general population, which is 1.62% (33). Another database in the UK suggests that there is a dose-dependent effect on fetal tetralogy at the concentration of 200 mg/ml. The two databases confirmed that there is increased occurrence of facial cleft. The incidence of facial cleft in newborns with pregnant women treated with lamotrigine is at the rate of 9.9/1,000 people, which is significantly higher when compared to the control rate of 2/1,000 people. A multitude of registries and databases have confirmed that there is a 2- to 3-fold increase in major malformations when there is *in utero* exposure to lamotrigine (34).

9. Phenytoin

Phenytoin is a hydantoin component which, when exposed *in utero*, can cause fetal hydantoin syndrome (FHS) in fetuses and newborns. This disorder causes and leads to multiple dysmorphic findings such as epicanthal folds, hypertelorism, broad flat nasal bridges, an upturned nasal tip, wide lips, distal digital hypoplasia, intrauterine growth retardation and mental retardation (35). A recent study showed that there was a prevalence of FHS in 11% of the children exposed to phenytoin *in utero* with 30% of the exposed children expressing at least some of the features of FHS. Therefore, the teratogenicity of phenytoin has been well-established (36).

10. Topiramate

Topiramate is a drug that is used for the treatment of epilepsy as well as migraines. While the data regarding the teratologic effects of topiramate is limited, a study has reported that the malformations resulting from its administration were at a rate of 4.8%, and when administered with other drugs (polytherapy), that number went up to 11.2%. The types of malformations resulting from topiramate include oral clefts and hypospadias, which were 11- and 14-fold higher, respectively, than the control (37). In addition, multiple cases of hypospadias, which is a birth defect of the urethra in males, have been reported for children that were exposed to topiramate *in utero* (38). The rates of major congenital

malformations are different from one study to the next. In a study conducted by Ornoy (29) 9.8% of fetuses were found to have malformation rate, which is double the rate reported by other studies (39,40). Researchers also found that pregnant women that were exposed to topiramate were found to have infants of lower birth weight as well as have a higher rate of spontaneous abortions (41). However, according to current literature, the rate of MCMs with exposure to topiramate is found to be similar to other AEDs.

11. Vigabatrin

Vigabatrin is an AED that is used specifically to treat specific refractoriness; its mechanism is to inhibit GABA-transaminase. While it is known that exposure to vigabatrin causes irreversible loss of vision in adult years, there is little research suggesting the consequence of its use in pregnancy. The scarce data available convey inconsistent findings of monotherapy exposure of vigabatrin (41). It was reported that approximately 15% of fetuses that were exposed to vigabatrin during pregnancy developed congenital malformations. There were some confounding factors in this study, including the fetal exposure to other AEDs. In addition, another study found that exposure to vigabatrin led to the malformation in children (42). However, once again, the women studied were also exposed to other AEDs. Finally, a study conducted by Turanli *et al* found no implications for children that were exposed to vigabatrin as fetus (43).

12. Conclusion

Appropriate management of epileptic pregnant women who are administered AEDs is important; seizure frequency may change during times like pregnancy, and both seizures and AEDs can have negative results for the fetus. We evaluated the effects of multiple AEDs including phenobarbital, valproic acid, carbamazepine, lamotrigine, phenytoin and topiramate. Some AEDs, such as valproic acid, are worse for the fetus than others. Newer AEDs, such as lamotrigine, need to be further evaluated in long-term studies for their effect on developing fetuses. Studies done on the use of phenobarbital suggests that it leads to a 4.3% increase in incidences of cleft palates in fetuses. Valproic acid administration was found to lead to neural tube defects, which lead to exencephaly. Study on carbamazepine found that it led to a 10-mm decrease in fetal head circumference. Administration of lamotrigine during pregnancy led to a 2- to 3-fold increase in major malformations. Phenytoin led to a 11% incidence of FHS in fetuses. Topiramate led to oral clefts at a 11-fold higher rate in fetuses. Putting aside valproate, the major congenital malformation rate for pregnant women taking AEDs is generally double that of women not on medication; the risk for women on AEDs for having children with malformations is approximately 4%. Hence, most pregnant women who are being administered AEDs will have no problems. Some ways to decrease the risk of birth defects are the use of folic acid and good obstetric care. Further studies are needed, however, to address cognitive effects of other AEDs; especially if these agents are used in increasing numbers during pregnancy (1,3-5).

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