Treatment options for epilepsy during pregnancy

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Women with epilepsy of childbearing age account for a third of the epilepsy population and about one in 200 pregnant women take antiepileptic drugs (AEDs). Although 90 to 95% of these women have an uneventful pregnancy with normal delivery of a healthy child (vs. 98% in the general population) there is a two to threefold greater risk of fetal malformation. The risk depends on the number of AEDs used and the type and dose of the drug – the risk appears higher with high doses of valproate than with older AEDs, such as carbamazepine and newer AEDs such as lamotrogine, but there is currently insufficient data on many of them. A familial history of malformation increases the risk but apparently not the number of seizures during pregnancy. Sudden interruption of AEDs can be life threatening for the fetus and the mother if withdrawal status epilepticus develops. More recently, psychomotor retardation has been observed in some infants born to women with epilepsy. Pregnancy in these women must be planned and monitored by a neurologist and an obstetrician.

Keywords: carbamazepine, epilepsy, gabapentin, lamotrigine, malformation, new antiepileptic drugs, oxcarbazepine, phenobarbital, phenytoin, pregnancy, primidone, psychomotor development, valproate, vigabatrin, zonizamide

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Epilepsy is one of the most common neurologic diseases, affecting approxiatemly 1% of the general population. As epilepsy frequently starts early in life, it is estimated that around a third of epileptic patients are women with epilepsy (WWE) of childbearing age. Therefore, about one out of 200 pregnancies thus occur in WWE, 80% of whom are taking antiepileptic drugs (AEDs) when they become pregnant. This proportion will undoubtedly rise in the future as indications for AEDs are broadened to include psychiatric diseases, chronic pain and migraine headache. It is also known that the frequency of unfavorable pregnancy outcome is higher in WWE than in the general population [1,2]. Several factors may contribute to this poor outcome including genetic factors, a direct chemical teratogenic effect of AEDs, or indirect effects via an interference with folic acid metabolism or other genetically determined pathways. The possibility of pregnancy, whether desired or not, must always be considered when prescribing AEDs for WWE of childbearing age. WWE should be given appropriate information and counseling very eary in life.

Pharmacologic considerations

Drug absorption, distribution and elimination are influenced by the dynamic physiologic changes that occur during pregnancy [3,4]. Nausea and vomiting that occur frequently during the first months of pregnancy may reduce the plasma level of AEDs. Intestinal motility is reduced by the increased plasma level of progesterone – this will increase the gastric and intestinal emptying by between 30 and 50%. There is a reduction by approximately 40% of gastric acid secretion. Any of these factors may alter the dissolution and absorption of the drug.

Drug distribution is modified – total body water is increased to 8 l, plasma volume expands by 50% [5] and blood flow is redistributed with an increase of uterine blood flow that reaches its peak at term (36–42 l/h) and a 50% increase in renal blood flow at the end of the 3rd month. As a result of these modifications, the maximal concentration (C_{max}) of many drugs will decrease.

Protein binding is also progressively decreased during pregnancy, as the plasma volume expands more than the albumin production [6,7]. Therefore the unbound pharmacologically active fraction of the drug is increased and thus more available for biotransformation. But while the plasma concentration will fall, the unbound concentration of the drug will remain relatively constant as a result of these different mechanisms.

Hepatic and renal elimination of AEDs may also be modified. The increased secretion of estrogen and progesterone affects hepatic metabolism in two ways [8]:

- Stimulation of hepatic microsomal enzyme activity with a higher rate of metabolism of certain drugs
- Inhibition of microsomal oxidases reducing hepatic elimination of some other drugs

However, it is extremely difficult to measure the extent to which a drug's hepatic metabolism is altered. Renal drug elimination is also modified as renal plasma flow increases by 30 to 50% and the glomerular filtration rate by 50% [9]. Elimination of drugs excreted via the kidney, such as gabapentin and vigabatrin could be enhanced, but there is not yet enough information on these new AEDs. In 12 women using lamotrigine monotherapy, de Haan and colleagues showed a gradual decline of the level-to-dose ratio to 40% of baseline during the second and third trimester [10]. This was associated with more frequent seizures in nine pregnancies. After delivery, lamotrigine kinetics returned swiftly to baseline, causing toxic effects in some women. Consequently, for WWE taking lamotrigine monotherapy, doses must be increased during pregnancy and decreased rapidly after delivery.

Fetal exposure to AEDs depends mainly on drug diffusion, the concentration gradient across the placental barrier (lipophilic drugs will cross more readily) and several factors influencing the placental barrier. Only unbound AEDs are capable of crossing the placental barrier. The main factors influencing placental permeability include:

- Maternal plasma concentration
- Placental blood flow
- Maternal versus fetal differences in plasma-protein binding
- Acid–base equilibrium

During pregnancy, the fetal albumin level will increase, changing its affinity for the drug during the maturation process. The drug is mainly eliminated via back diffusion from the fetus to the mother; however, metabolic processes are active in the fetal liver as early as the 8th week post conception (marginally at the beginning) [11]. Metabolites are less likely to cross the placental barrier as they are more polar than their parent compound and may accumulate in some fetal tissues [3]. Routine drug monitoring usually targets older AEDs, generally by measuring total plasma concentration rather than the pharmacologically active unbound concentration. Drug monitoring is generally not a routine practice for the new AEDs (although reliable assays are available); however, monitoring plasma lamotrigine during pregnancy should be routine, as suggested by de Hann and colleagues [10]. This could help to adapt the doses; however, many would advise only adjusting the dose if there was evidence for an increase in seizures.

Folate deficiency is a potential mechanism of AED teratogenicity as most AED therapies induce cytochrome P450 metabolism leading to a folate blood level reduction. The recommended daily allowance of folate increases from 0.4 to 0.6 mg/day in pregnant women. The increased folate catabolism during pregnancy, AED use and individual variation of requirements, has led some to call for higher folate supplementation.

Teratogenicity

The first conclusive report of anticonvulsant teratogenicity was a letter by Meadow, describing six cases in 1968 [12]. The general estimate is that there is a two- to threefold risk in the general population. Among recent reports, Kaneko and colleagues prospectively followed 983 pregnancies in WWE and found that the rate of fetal malformations was 9% among those treated with AEDs and 3.1% among the untreated women [13]. In the Australian registry published in 2003, among 292 term pregnancies in WWE, the rate of significant fetal malformations was 7.9% (including four voluntary terminations after ultrasonographic discovery of malformation) [14]. The rate of spontaneous abortion was 3.6%, probably related in part to fetal malformations.

Methodologic difficulties

The higher risk of malformation is related to several factors. Some, such as genetic risk, are uncontrollable, while others, such as the frequency of seizures during pregnancy or the use of AEDs, are theoretically controllable. The mechanisms by which AEDs could favor the development of malformations remains unclear. Certain AEDs interfere with folic acid metabolism implicated in neural tube closure. This could be the mechanism by which sodium valproate and carbamazepine induce spina bifida.

It is very difficult to study the mechanisms of these malformations because of numerous methodologic biases reviewed by Dolk and Elhatton [15]. All of the published data have come from observational studies. None of the studies randomized women for AED prescription, drug dose or type, and were not controlled for ethical and practical reasons. Furthermore, epilepsy features a wide range of conditions with highly variable severity depending on the recruitment. Consequently, the study group can be different from the control group. Methodologic biases also impair comparisons between the general population and WWE because different

methods are used to measure malformations; however, the same methods are used in the same study for measuring outcomes between controls and the cohort, this relates more to the inter study comparisons. Searching for genetic causes requires studying the children of epileptic men. Confirming the role of any given drug means it would have to be studied in association with a specific malformation, with a search for a dose effect. Differentiating the drug from the seizure effect would require a control population of nonepileptic subjects taking the same drug for another reason, such as pain. Unfortunately each of these issues would require a very large-scale study, possible only in a multicenter setting. Pregnancy registries, recommended by the International League Against Epilepsy, have been developed to provide prospective information on WWE, AED and pregnancy. The principal registries are listed in **Table 1**. Registries have also been organized for other purposes, such as the International Registry of Pregnant Women taking Lamotrigine [16].

Role of seizures

Several studies have suggested that epileptic seizures themselves could be the cause of fetal malformations, especially if they occur during the first trimester of pregnancy. These studies had many methodologic flaws, and several more recent prospective studies have demonstrated that the type of seizure, their frequency and the presence or absence of generalization are apparently unrelated to the major teratogenic effect [2,17]. Consequently, striving to achieve rigorous control to prevent seizures with higher doses or repeated administrations of AEDs would be useless and even dangerous. In a recent study, Vinten and colleagues found that a neuropsychologic parameter (verbal intelligence quotient [vIQ]) could be affected if the mother had more than five generalized seizures during pregnancy [18]. As shown in major prospective studies, WWE not taking AEDs do not have an increased risk of malformations [2–4,10–13].

Table 1. Main pregnancy registers currently available.

Country	Period of time analyzed	Number of pregnancies	Ref.
Australia	July 1999 to December 2001	334	[14]
North America	1997 to 2002	3002	[20]
International	Through 2004 May	2238	[39]
United Kingdom	Through 2004 August	4000	[40]

Mono- versus polytherapy

Several studies have shown that teratogenicity increases with polytherapy and high doses compared with monotherapy and low doses (**Figure 1**). Recent studies have confirmed the earlier findings.

Older drugs

At least in the prospective studies, it is not possible to link significantly the type of malformation with a specific AED [13]. The older cases reported in the literature are summarized in **Table 2**. Similarly, there is no evidence of a significant difference in the incidence of malformations in offspring exposed to a single older AEDs (i.e., phenobarbital, primidone, phenytoin, carbamazepine) [13], except for valproate in the most recent reports. Among the pregnancy registry studies, Holmes and colleagues reported that 6.5% of 77 pregnancies with exposure to phenobarbital were associated with major malformation compared with a 1.62% background rate [19]. Wyszynski and colleagues reported a prospective study where, assuming a 1.62% risk in the control group, the relative risk of having a child with major malformation for valproate monotherapy-exposed women in the first trimester of pregnancy was 7.3% (confidence interval [CI]: 4.4–12.2; $p < 0.001$) [20]. The daily dose of valproate used is, for different authors, an important issue in the occurrence of a major malformation – for Samren and colleagues the relative risk is 7 in WWE taking more than 1000 mg/day and 1 for WWE under the daily dose of 600 mg/day [21]. For Kaneko and colleagues the blood dosage of valproate is higher in WWE bearing children with a major malformation than in WWE with normal children (77.8 ± 20 and 46.9 ± 21 µ/ml, respectively) [13].

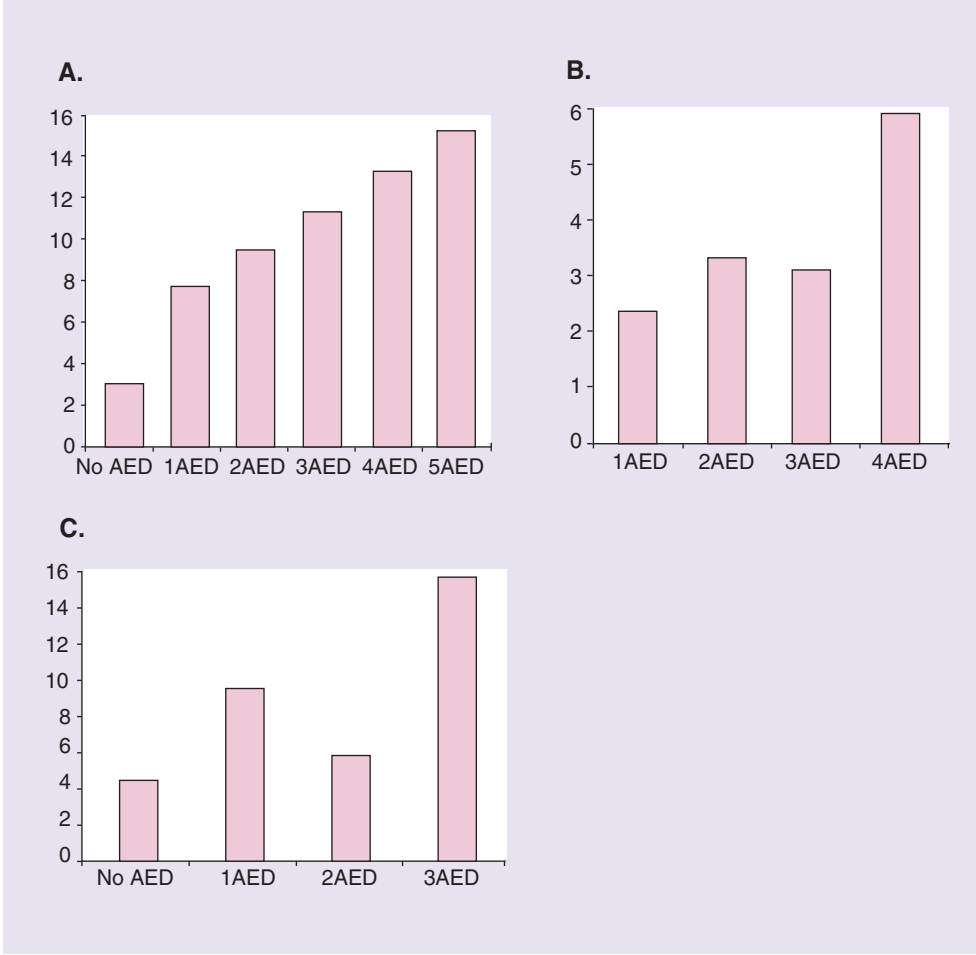
New antiepileptic drugs

The main data are summarized in **Table 3**. Felbamate and vigabatrin are not included in this table because indications are very restrictive. Tiagabine is rarely used. It seems that the malformation rate could be lower with lamotrigine [16–22] and similar to that of the general population (among 414-first trimester exposure), but more data is required to conclude definitively, as lamotrigine levels may fall during pregnancy – toxicity may be reduced, but seizures may still increase.

Prevention

Prevention of fetal malformations implies planning reproduction before conception. The patient should be referred to a neurologist to

Figure 1. Relative risk of fetal malformation by number of antiepileptic drugs.



(A) Results of a study by Samren and colleagues in 1411 children [17], **(B)** Results of a study by Kaneko and colleagues in 983 pregnancies [13], and **(C)** Results of a study by Vajda and colleagues in 256 children [14].
AED: Antiepileptic drug.

examine the need for AED treatment. If a WWE desiring pregnancy requires an AED, every effort should be made to achieve control with a single drug given at the lowest dose possible. Whilst current knowledge does not allow the use of the AED with the least teratogenic risk, valproate should be avoided, especially in doses above 1000 mg/day. Adjuvant folic acid is recommended to prevent spina bifida and orofacial clefts [23,24], even though there is no sound evidence of efficacy in this population. All available studies have been conducted in nonepileptic subjects. A dose of 0.4 to 4 mg appears to be sufficient [25]. Patients receiving polytherapy, particularly with enzyme-inducing AEDs, may require higher doses to maintain sufficient folate blood levels [26]. The prescription should begin before conception since major malformations appear during the first weeks of pregnancy.

Risk of psychomotor retardation

In recent years there has been much work on the risk of psychomotor retardation, but several years of follow-up are required to obtain pertinent data. Mental retardation is defined as the proportion of children requiring special education and having lower results in psychometric tests (mainly Weschler) [18,27,28]. Katz and colleagues showed pervasive developmental delay in 6.2% of offspring of 100 WWE, but statistical power was insufficient to identify risk factors [29]. Vinten and colleagues performed neuropsychologic investigations in 249 children of WWE between the ages of 6 and 16 years [18]. Children exposed to sodium valproate had a significantly lower vIQ when compared with children exposed to other AEDs or not exposed at all. The same children were more likely to have an IQ below 69 and more likely

Table 2. Teratogenicity of antiepileptic and classical drugs [13,21].

Drug name	Frequency of use (%)	Frequently observed malformations	Dose-related effect
Phenobarbital	5.1–10.0	Cardiac malformations and facial clefts.	Yes
Phenytoin	6.0–11.1	Fetal phenytoin syndrome: growth retardation, small cranial diameter, facial dysmorphic facies, cleft palate, cardiac malformations and distal digital hypoplasia with small nails. Holoprosencephaly (more rarely): chondrodysplasia punctata-like syndrome with flat facies and stippled epiphyses.	
Valproate	9.0–11.1	Fetal valproate syndrome [41]: dysmorphic facies, neural-tube defect, cleft palate, radial ray defect (rare but specific), cardiac malformations and ophthalmological problems.	Yes
Carbamazepine	5.7–8.0	Dysmorphic facies (less marked than with valproate), neural tube defect, cardiac malformations, hypospadia and nail hypoplasia.	

to have memory impairment when compared with the other groups. Exposure to sodium valproate was a significant predictor of low vIQ in this population. Whilst Vinten and colleagues mentioned the significance of dose effect in previous reports, it was not suggested in the aforementioned paper. Furthermore, they did not determine whether the risk was different for exposure during the first trimester or later, nor whether malformations were associated. Their data showed that the IQ of the mother and the presence of more than five generalized tonic–clonic seizures during pregnancy in WWE were also factors significantly predictive of low vIQ in their children. Gaily and colleagues demonstrated in 182 children born to WWE that exposure to sodium valproate during pregnancy and polytherapy were associated with lower vIQ, while children exposed to carbamazepine had normal neuropsychologic tests [27].

Aggravation of epilepsy

Malformations appear to be much more related to use of AEDs than to epileptic seizures, but on the contrary, fetal and maternal mortality is much higher in WWE. In the UK between 1985 and 1999, there were around 1000 deaths from 11 million pregnancies – approximately 50 of these were to WWE – making epilepsy the third most common cause of indirect death after cardiac deaths and stroke. This corresponds to a tenfold increase in mortality for pregnant WWE. Most of these deaths are seizures or status related and probably related the discontinuation of an AED [1]. Consequently, when pregnancy is diagnosed in WWE, abrupt interruption of their AED is a major error. Embryonic organogenesis is generally terminated when a woman realizes she is pregnant and consults her physician. It is also known that sudden withdrawal of AEDs is an important risk factor favoring repeated seizures and status epilepticus. In the event of status epilepticus, fetal death would occur in 50% of cases and maternal death in 30% [30]. Fetal morbidity in epilepsy is largely related to the mechanical risks of falling and convulsions during the later stages of pregnancy, seizures occurring during delivery and to status epilepticus. Convulsions during delivery are a particular problem as they have resulted in maternal death and fetal asphyxia. A total of 1 to 2% of WWE have a convulsion during delivery [31], a risk lowered by therapy. Unfortunately, pregnant WWE may not comply optimally with drug prescription. As drug companies warn women to minimize or avoid drug use during pregnancy, the perception of the teratogenic risk may be unrealistic and misinformed pregnant women may tend to comply less with their drug therapy.

Obstetric problems

It has been mentioned previously that children of WWE may have intrauterine growth restriction, with a risk of preterm delivery and low birth weight as well as potential consequences far beyond childhood [32,33]. Richmond and colleagues found that the risk of nonproteinuric hypertension and provoked delivery were increased, but that the rates of other antenatal, intrapartum and neonatal complications were similar to those of control subjects [34]. The occurrence of major antepartum seizures did not increase the rate of adverse outcomes significantly. In a study of 193 WWE, the risk of preterm delivery was only increased in WWE who smoked compared with healthy women who smoked [35]. Birth weight was also reduced in WWE with treatment. The risk of neonatal hemorrhage, particularly with enzyme-inducing AEDs, was demonstrated in earlier

Table 3. Teratogenicity of new antiepileptic drugs.

Drug	No. of births	Malformations on monotherapy (%) (no. of births)	Spontaneous abortions (%)	Malformations on polytherapy (%) (no. of births)	Note	Ref.
Lamotrigine	684	2.9 (414)	0.0	12.5 (88) with valproate 2.7 (182) without valproate	Only first trimester exposure was taken into account	[16]
	51				2% of malformation, for mono- and polytherapy	[22]
Zonisamide	26	0.0 (4)		7.7 (2)		[42]
Oxcarbazepine	55	0.0 (35)	0.0	5.0 (20)	Cardiac malformation under bitherapy (oxcarbazepine and phenobarbital)	[43]
	37				6.5% of malformations, for mono- and polytherapy	[22]
Levetiracetam	3	0.0 (3)	0.0			[44]
	11	0.0 (2)	22.0	0.0 (7)	Low birth weight in 27%	[45]
Gabapentin	44		13.7		6.5% of malformations, for mono- and polytherapy	[46]

studies. Kaaja and colleagues published a recent study where the data did not support the hypothesis that maternal enzyme-inducing AEDs increased the risk of bleeding in the offspring [36]. However, in selected cases, in particular when other risk factors are present, preventive measures may still be required – such as a pediatrician or an intensive care unit at proximity.

Pregnancy monitoring & delivery

Pregnancy should be carefully monitored in WWE, as in other women. The only special precaution is to perform supplementary ultrasound examinations very early in order to establish term as precisely as possible. Another anatomic ultrasonography is recommended at week 12 to identify severe defects. The ultrasonography is repeated at weeks 16 and 22 to identify other malformations and later to monitor fetal growth. Special care must be taken to explain the necessity of the prescribed treatment and patient compliance. The lesser risk of malformations after the 4th month can leave more room for adjusting the treatment.

Vaginal delivery is desirable for most WWE. As stress, pain, lack of sleep and poor drug compliance are factors that can lower the seizure threshold, there is no contraindication for peridural anesthesia, which can be recommended for pain and stress relief. It is preferable, depending on the treatment, for a pediatrician to be present in the delivery room in order to assure surveillance of the newborn at risk of withdrawal syndrome. The AED treatment should be continued after delivery, sometimes with dose adaptation as for lamotrigine.

Breastfeeding

To some degree, all AEDs are secreted in the mother's milk. The more recent AEDs bind less to plasma proteins and thus are found in higher concentrations in human milk. The benefits of breastfeeding and progressive withdrawal for the infant must be balanced against the possible deleterious effects on the developing brain – as no evidence can be claimed regarding breastfeeding and its possible deleterious effects, the debate is still open. Liporace and colleagues demonstrated in a limited number of patients that high levels of lamotrigine in breastfed newborns were related to major excretion in milk and insufficient glucuronidation, but no clinical symptom was found in the newborn [37]. Data from animal studies and one clinical case suggest that levetiracetam (LEV) is also excreted in large quantities in milk [4]. Another recent study found a milk/maternal serum concentration ratio of LEV was 1.00 (range 0.76–1.33), but breastfed infants had a very low LEV concentration [38].

Conclusions

The increased rate of congenital malformation in children of WWE is mainly caused by AEDs. For WWE consulting before pregnancy, the first step is to check whether the current AED treatment is necessary. A switch from poly- to monotherapy should be tried. An attempt should be made to lower the AED dose, particularly when sodium

valproate is used, and doses above 1000 mg/day or 70 µg/ml should be avoided. Slow release forms of AEDs should be preferred – dividing daily intake into three to four equal doses could be another solution to avoid the plasma peak of the drug. Regular obstetric and ultrasonographic surveillance should be scheduled with a second evaluation of the antiepileptic treatment after the first trimester. No special precaution is required for delivery. It would be useful to conduct follow-up studies of infants born to WWE in order to search for mid-term cognitive disorders.

Outlook

Pregnancy registers will be helpful in the future to obtain more precise information regarding pregnancy in WWE taking AED and in particular fetal malformations. Clarifying the issue of developmental delay in children of WWE will require long-term follow-up of large cohorts. In specific at-risk populations, multidisciplinary consultations should be proposed before pregnancy to choose the most appropriate drug regimen and to plan pregnancy follow-up.

Highlights

- Approximately a third of epileptic patients are women with epilepsy (WWE) of childbearing age – one pregnancy out of 200 occurs in women taking antiepileptic drugs (AEDs).
- Pregnancy is uncomplicated with normal outcome in 90 to 95% of WWE taking AEDs (vs. approximately 98% in the general population).
- Studies raise difficult methodologic problems and require large cohorts. The International League Against Epilepsy recommends national or international pregnancy registries.
- Sudden interruption of antiepileptic medication can be life threatening for the fetus and the mother due to the risk of status epilepticus.
- Fetal malformations:
  - A two- to threefold higher risk than in the general population.
  - Depends on the type of AED used, the number of drugs and their doses. The risk seems to be higher with sodium valproate especially with high doses (>800 mg/day) and appears to be lower with more recent AEDs, but data are sparse.
  - A family history of malformation increases the risk of fetal malformation in WWE.
  - Having seizures during pregnancy does not appear to increase the risk of malformation.
  - A history of epileptic seizure or untreated epilepsy does not increase the risk of fetal malformation.
- More recently, psychomotor retardation has been observed in children born to WWE. Sodium valproate has been incriminated but other risk factors and confounding factors remain to be elucidated.
- Breastfeeding:
  - All AEDs are secreted in the mother's milk.
  - The benefits of breastfeeding and progressive withdrawal for the infant must be balanced against the possible deleterious effects on the developing brain.
  - There are differences in opinion about breastfeeding that illustrate the limitation of the evidence, but WWE should in general be encouraged to breastfeed their infants.
- Pregnancy should be planned and monitored, with a neurologist and obstetrician working collaboratively.

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