

PREGNANCY AND REPRODUCTIVE HEALTH IN PATIENTS WITH EPILEPSY

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INTRODUCTION

Treatment during pregnancy in women with epilepsy involves a precarious balancing act between the teratogenic risks of antiepileptic drugs (AEDs) and maintaining maternal seizure control. However, pregnancy registries and other prospective studies have given us invaluable information on how to optimize treatment regimens for the safety of the mother and for the developing fetus. These detailed data should be a key consideration when counseling and treating women with epilepsy.

CONTRACEPTION

From the initial clinical appointment and repeated at every subsequent visit, the AEDs prescribed should be considered in light of the risks of the medications during any potential pregnancy, planned or unplanned, as well as the potential for interactions with contraception medications. Effective contraception in women with epilepsy is essential to allow for preconception planning and to implement the measures known to improve pregnancy outcomes. However, concomitant use of AEDs and hormonal contraceptives is complicated because of the bidirectional pharmacokinetic interactions and the pharmacodynamic consequences. The enzyme-inducing AEDs lead to rapid clearance of sex steroid hormones and may allow ovulation in women taking oral contraceptives (OCs) or other hormonal forms of birth control (vaginal ring, patch). Table 1 categorizes the different AEDs according to the degree of induction of female sex steroid hormones (SSH). The CDC Medical Eligibility Criteria for contraception classified certain AEDs (phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB), primidone (PRM), topiramate (TPM), and oxcarbazepine (OXC)) as a Category 3: the risks (birth control failure) generally outweigh the benefits (1). The authors state that the use of other contraceptives should be encouraged for women who are long-term users of any of these drugs. For women on EIAEDs that cause substantial changes in SSH levels, one of the Long-Acting Reversible Contraceptives (LARC) should be encouraged. These include intramuscular medroxyprogesterone acetate, and the intra-uterine devices (IUDs). Although the progestin implant is also a LARC, it should not be used in combination with strong EIAEDs as pregnancies have been reported with CBZ and OXC concomitant use.

FERTILITY

Most studies of women with epilepsy suggest lower birthrates to women with epilepsy, with only 37% to 88% of comparison groups (26,27). Findings persisted when analyses were limited to married women. In contrast, the Northern Finland Birth Cohort reported epilepsy women did not differ from the reference group with respect to number of children, but epilepsy not in remission was associated with fewer children (28,29). None of these studies collected information about the desire or attempts to achieve pregnancy. A survey of childbearing-aged epilepsy women in the UK reported 33% of the respondents were not considering having children because of their epilepsy³. Birth rates could be lower in women with epilepsy due to social factors such as lower marriage rates and lower rates of seeking pregnancy, and/or due to physiologic factors such as diminished libido or lower ovulatory rates. No prior studies had prospectively compared epilepsy women to healthy women attempting to conceive until the WEPOD study. Women with Epilepsy: Pregnancy Outcomes and Deliveries (WEPOD) was a multi-center prospective, observational study, comparing fertility in epilepsy women to healthy controls. Among 89 epilepsy women, 60.7% achieved pregnancy vs. 60.2% for 108 controls. Median time to pregnancy was no different after controlling for key covariates. Sexual activity and ovulatory rates were similar in both groups, and 81.5% of pregnancies resulted in live births in both groups. In conclusion, epilepsy women seeking pregnancy had comparable likelihood of achieving pregnancy, time to

pregnancy, and live birth rates compared to a group of healthy peers. However, women on EIAEDs showed a trend toward a negative impact on fertility and needs further study. Overall, these findings should reassure women and clinicians when counseling women who are planning pregnancy (30).

PREGNANCY

Epilepsy is the most common neurologic disorder that requires continuous treatment during pregnancy and AEDs are one of the most frequent chronic teratogen exposures. Approximately one-half million women with epilepsy are of childbearing age in the US and 3–5 births per thousand will be to women with epilepsy (2). However, it is estimated that the total number of children in the US exposed *in utero* to AEDs is substantially greater with the emergence of AED use for other illnesses including headache, chronic pain, and mood disorders. The three-part series of AAN Practice parameter updates on the topic of pregnancy in women with epilepsy published in 2009 provide a comprehensive synthesis of information published up to that date, and additional key reports published since then will also be highlighted below (2-4).

MAJOR CONGENITAL MALFORMATIONS

Offspring of women with epilepsy on AEDs are at an increased risk for major congenital malformations (MCMs), an abnormality of an essential anatomical structure present at birth that interferes significantly with function and/or requires major intervention. The reported MCM rates in the general population vary between 1.6 - 3.2 %, and women with a history of epilepsy on no AEDs show similar MCM rates. The average MCM rates among all AED exposures vary between 3.1% - 9%, or approximately 2-3 folds higher than the general population (2, 5). By the time most women realize they are pregnant, it is too late to make medication adjustments to avoid MCMs.

AED Monotherapies: Data obtained from large, prospective pregnancy registries from different parts of the world have demonstrated remarkably consistent findings for many of the AEDs. The 2009 AAN Practice Parameter updates on “Management issues for women with epilepsy – focus on pregnancy” (2) led to many important conclusions about intrauterine first trimester exposure and risk for MCMs: 1) It is highly probable that valproic acid (VPA) exposure has higher risk of MCMs compared to CBZ and possible compared to PHT or lamotrigine (LTG), 2) compared to untreated WWE, it is probable that VPA as part of polytherapy and possible that VPA as monotherapy contribute to the development of MCMs, 3) it is probable that AED polytherapy as compared to monotherapy regimens contributes to the development of MCMs, 4) CBZ probably does not substantially increase the risk of MCMs in the offspring of WWE, and 5) there is probably a relationship between the dose of VPA and LTG and the risk of development of MCMs in the offspring of WWE. Additionally, for specific types of MCMs, findings included: 1) PHT possibly contributes to the risk of cleft palate, 2) CBZ possibly contributes to the risk of posterior cleft palate, 3) VPA probably contributes to neural tube defects and facial clefts and possibly contributes to hypospadias, and 4) PB exposure *in utero* possibly contributes to cardiac malformations.

Since this evidence-based review of the literature, several large prospective pregnancy registries continue to provide valuable information. They reveal a very consistent pattern of amplified risk for the development of MCM in pregnancies exposed to VPA. The registries have also provided updated information on additional AEDs. The UK Epilepsy and Pregnancy Register reported on findings with TPM use in 178 live births (6). Although the confidence intervals were wide, this preliminary information noted a MCM rate of 4.8% for monotherapy use, and even higher for use of TPM as polytherapy. They also noted a particularly higher rate of oral clefts and a high rate of hypospadias. The risk of oral clefts with TPM has been replicated in other studies (7).

The North American AED Pregnancy Registry released findings comparing the risk of MCM among infants exposed to different AED monotherapies during the first trimester, as well as to an unexposed reference group (8). The LTG monotherapy group was chosen as the exposed reference group for the other AEDs because of a low MCM rate and tight confidence intervals (2.0 % [95% CI 1.4-2.8]). These reported findings can serve as a particularly instructive tool during the preconception counseling phase of women with epilepsy, with detailed information on many of the AEDs and calculation of confidence intervals for the risk numbers presented (Table 2). Additional analysis included the risk of MCM by average daily VPA dose during the first trimester and confirms prior reports of a dose-related risk for VPA and MCM. However, the upper limit of the confidence intervals for the lowest VPA daily dosage group (<500 mg) reached over 7% and this low range is an uncommon dose to maintain seizure control. Hernandez-Diaz, et al. (8) also examined the frequency of specific MCMs for each AED, and reported that VPA was associated with an increased risk of hypospadias, neural tube defects, and cardiovascular malformations, PB with an increased risk of cardiovascular malformations, and PB, VPA, and TPM with an increased risk of oral clefts, consistent with previous reports.

The UK and Ireland Epilepsy and Pregnancy Registers combined results for first trimester exposure to levetiracetam (LEV) with outcome data (9). The MCM rate in the LEV monotherapy group was 0.70% (95% CI: 0.19%-2.51%) and in the polytherapy group was 5.56% (CI: 3.54%-8.56%); the MCM rate in the polytherapy group was lower when LEV was given with LTG (1.77%; CI 0.49%-6.22%) than when given with VPA (6.90%; CI 1.91%-21.96%) or CBZ (9.38%; CI 4.37%-18.98%).

A report from the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) confirmed that in addition to the type of AED, dose of the AED at conception also affects rates of MCMs (10). MCM rates in pregnancies exposed to CBZ, LTG, VPA, and PB were analyzed by dose at time of conception (not throughout the first trimester or entire pregnancy). The lowest rates of MCMs occurred with LTG <300mg/day (2.0%; 95% CI 1.19–3.24), and this group was used as the comparator group. Risks of MCMs were higher with VPA and PB at all doses, and with CBZ at >400mg/day. Additionally, an increase in MCM rates was observed with increasing doses for all four AEDs, in support of the concept that the amount of fetal exposure to an AED is important, as well as the type of AED. Therefore, reduction of the dose prior to conception while maintaining seizure control can further reduce the risk of structural teratogenicity. Determining the women's individual target concentration preconception can be a valuable tool for therapeutic drug monitoring during pregnancy (see below).

AED Polytherapy: The rates of MCMs have been reported as higher across several studies for women on AED polytherapy compared to AED monotherapy regimens (2). These results led to the recommendation that AED monotherapy is preferred to polytherapy during pregnancy and should be achieved during the preconception planning phase (2). However, the North American AED Pregnancy Registry reported that not all AED polytherapy combinations are alike (11). Both LTG and CBZ had relatively modest rates for MCMs if the polytherapy combination was with any AED other than VPA. The MCM rates were 9.1% for LTG plus VPA (OR, 5.0; 95% CI 1.5-14.0) but only 2.9% for LTG with any other AED (OR 1.5; 0.7-3.0); likewise, the risks were 15.4% for CBZ plus VPA (OR, 6.2; 95% CI, 2.0-16.5) and 2.5% for CBZ plus any other AED (OR 0.8; 95% CI 0.3-1.9).

NEURODEVELOPMENTAL OUTCOMES

Studies investigating cognitive outcome in children of women with epilepsy report an increased risk of mental deficiency (2). The 2009 AAN Practice Parameter Updates reported the following conclusions about *in utero* exposure (throughout the entire pregnancy) and risk for poor cognitive outcomes (3): 1) Cognition is probably not reduced in children of untreated WWE, 2) CBZ probably does not increase poor cognitive outcomes compared to unexposed controls, 3) monotherapy exposure to VPA probably reduces cognitive outcomes, 4) monotherapy exposure to PHT or PB possibly reduces cognitive outcomes, and 5) AED polytherapy exposure probably reduces cognitive outcomes as compared to AED monotherapy.

Since the 2009 AAN Practice Parameter update, several notable reports have been published. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study was a prospective, observational, multicenter study in the US and United Kingdom, and assessed the neurodevelopmental effects of *in utero* exposure to four monotherapy groups (CBZ, VPA, PHT, and LTG) (12). The primary outcome was intelligence quotient (IQ) at age six years-old. Multivariate analysis demonstrated that the VPA-exposed children had lower age-6 IQ compared to CBZ, LTG or PHT, and they did poorly on several specific measures. High doses of VPA were negatively correlated with IQ, verbal ability, non-verbal ability, memory, and executive function while the other AEDs did not have a dose-effect. Interestingly, mean IQs were higher in the children of mothers who took periconceptional folic acid. This key evidence of a beneficial effect of supplemental folic acid taken prior to and early in pregnancy in women with epilepsy on AEDs supports the recommendation that all women of childbearing age should be encouraged to take supplemental folic acid, especially in light of the high unplanned pregnancy rate.

The neurodevelopment research group from Liverpool and Manchester also reported that children that were exposed to VPA *in utero* had a higher prevalence of neurodevelopmental disorders (13). Moreover, autism spectrum disorder (ASD) was the most frequent diagnosis for the VPA-exposed children. A population-based study from Denmark found that in the children exposed to VPA, an absolute risk for autism spectrum disorder of 4.42% (95% CI, 2.59%-7.46) (adjusted HR, 2.9 [95% CI, 1.7-4.9]) and an absolute risk of 2.50% (95% CI, 1.30%-4.81%) for childhood autism (adjusted HR, 5.2 [95% CI, 2.7-10.0]) (14).

Neurodevelopmental outcomes for LEV have recently been published by the Liverpool and Manchester Neurodevelopment Group with the United Kingdom Epilepsy and Pregnancy Registry (15). After adjusting for confounding variables, children exposed to VPA *in utero* scored lower on measures of gross motor skills, comprehension language abilities, and expressive language abilities compared to children exposed *in utero* to LEV. Children exposed to LEV *in utero* did not differ from the unexposed control children.

In summary, if you choose to place an adolescent or adult woman of childbearing age on VPA, you are putting her potential children at a substantially greater risk for major congenital malformations, lower IQ, and autism spectrum disorder.

NEONATAL COMPLICATIONS

Recent reports suggest that there may be increased risk for other neonatal complications for offspring of women with epilepsy on AEDs. Findings from the 2009 AAN/AES Practice Parameter Update concluded the following (2): 1) Neonates of WWE taking AEDs probably have an increased risk of being small for gestational age (SGA) of about twice the expected rate and 2) neonates of WWE possibly have an increased risk of a 1-minute Apgar score of <7 of about twice the expected rate. Since this parameter was released, a study from Taiwan reported that seizures in mothers with epilepsy during pregnancy were independently associated with approximately a 1.5-fold increased risk for preterm delivery or infants being born small for gestational age (SGA) (16). The North American AED Pregnancy Registry reported that prenatal exposure to TPM or ZNS was associated with higher risk for SGA births compared to prenatal exposure to LTG (17).

SEIZURES DURING PREGNANCY

The effect of pregnancy on seizure frequency is variable. Approximately 20-33% of patients will have an increase in their seizures, 7-25% a decrease in seizures, and 50-83% will experience no significant change. EURAP reported on a large, but selective cohort of WWE entering pregnancy on monotherapy (18). Two-thirds of women remained seizure-free throughout pregnancy, and women with genetic generalized epilepsies were more likely to remain seizure free than women with localization-related epilepsies. Generalized tonic-clonic convulsions (GTCC) can cause maternal and fetal hypoxia and acidosis, fetal heart rate decelerations, and have been associated with miscarriages and stillbirths. Nonconvulsive seizures can cause trauma, which can result in ruptured fetal membranes with an increased risk of infection, premature labor, and even fetal death. Additionally, reemergence of seizures in a woman who had previously experienced seizure control can be devastating.

More recent reports have highlighted the potentially higher maternal and obstetric risks during pregnancy, although the methods of the studies have not been able to clearly associate seizures as the primary cause. For example, a recent retrospective cohort study report utilizing delivery hospitalization records from the 2007-2011 Nationwide Inpatient Sample reported that women with epilepsy were at higher risk for several adverse outcomes including preeclampsia, preterm labor, stillbirth, increased health care utilization, including an increased risk of cesarean delivery, most with adjusted odds ratios (OR) around 1.5, but with even higher OR of > 2.0 for prolonged length of hospital stay (>6 days) with cesarean deliveries and with vaginal deliveries. Even more striking was the finding that women with epilepsy had a risk of death *during* delivery hospitalization with an adjusted odds ratio [OR] of 11.46 [95% CI, 8.64-15.19], although to put this in perspective the baseline rate was 6 deaths per 100 000 pregnancies among women without epilepsy and 80 deaths per 100 000 pregnancies for women with epilepsy. The methods of this study did not allow evaluation of key factors, including verification of epilepsy diagnosis, evaluation of seizure frequency, severity or proximity, cause of maternal mortality, and if mortality was more likely to be associated with seizures, AEDs used, or other factors. Future prospective studies of well-defined cohorts will help to sort out potential contributing factors to these increased peripartum risks.

AED MANAGEMENT DURING PREGNANCY

Maintaining seizure stability during pregnancy is dependent on maintaining therapeutic concentrations of the baseline AED. The target concentration should be individually determined, ideally in the preconception phase, for each woman according to her epilepsy history and prior seizure control relative to AED concentrations. During pregnancy, management of the AED dosing becomes complex and requires a more intensive approach than during non-pregnant stages. Clearance of most of the AEDs increases during pregnancy, resulting in a decrease in serum concentrations (Table 3) (3, 19). The 2009 AAN/AES Practice Parameter Update concluded the following: Pregnancy probably causes an increase in the clearance and a decrease in the concentration of LTG, PHT, and to a lesser extent CBZ, and possibly decreases the level of LEV and the active OXC metabolite, the monohydroxy derivative (3).

The magnitude of enhanced clearance of LTG during pregnancy exceeds that described for many of the older AEDs, as hepatic glucuronidation is particularly susceptible to activation during pregnancy due to the direct effects of rising sex steroid hormone levels. In the prospective EURAP registry, pregnancies on LTG monotherapy were less likely to be seizure-free (58.2%), had a greater likelihood of deterioration in seizure control from the first to the second or third trimesters (19.9%), and were more likely to require an increase in drug load (18). Pennell et al. reported that both LTG free and total clearance were increased during all three trimesters, with peaks of 94% (total) and 89% (free) in the 3rd trimester (20). The authors reported that seizure frequency significantly increased when the LTG level decreased to 65% of the preconception individualized target LTG concentration. This finding supports the recommendation to consider monitoring levels of LTG and other AEDs for which clearance increases during pregnancy (3).

Previous studies on LTG noted a rapid decrease in LTG clearance during the early postpartum period with reports of symptomatic toxicity. Pennell et al. (20) also examined the effectiveness of using an empiric postpartum taper schedule for LTG, with steady decreases in dosing at postpartum days 3, 7, and 10, with return to preconception dose or preconception dose plus 50 mg to help counteract the effects of sleep-deprivation. Patients were assessed for symptoms of LTG toxicity. Non-adherence to the standard taper schedule was associated with significantly higher risk of experiencing postpartum toxicity. Most of the other AEDs levels gradually increase after delivery and plateau by 10 weeks postpartum. The exact time course is not as well established for the other AEDs, but AED doses should be adjusted and/or levels should be followed during the postpartum period.

BREASTFEEDING

Most infants of women with epilepsy can successfully breastfeed without complications. The concentrations of the different AEDs in breast milk are less than those in maternal serum for many of the AEDs, and when infant's serum concentrations have been measured, they are significantly less than maternal paired serum concentrations (3,21,22). The benefits of breast-feeding are believed to outweigh the small risk of adverse effects of AEDs. Recent data from the NEAD cohort actually demonstrated a benefit to breastfeeding ; adjusted IQ was actually higher by 4 points for children who were breastfed vs. those who were not (23).

SUMMARY

Planned pregnancies are essential to improve maternal and fetal outcomes for women with epilepsy. The consistent findings of increased risk for major congenital malformations and neurodevelopmental deficits with VPA use during pregnancy should be a primary consideration in treatment decisions, as well as the newer findings of differential risks between types and doses of the other AEDs. Folic acid supplementation should be encouraged in all women of childbearing age on any AED. Maintaining seizure control during pregnancy is important, and therapeutic drug monitoring of serum AED levels can help achieve that goal, especially for AEDs that undergo substantial pregnancy-associated changes in clearance. Knowledge and appreciation of these key principles enhances our ability to make informed treatment recommendations that not only provide favorable seizure control, but also improved maternal and child outcomes.

Table 1. Antiepileptic Drugs: Degree of Induction of Metabolism of Hormonal Contraceptive Agents

Strong Inducers*	Weak Inducers*	Non-inducers
phenobarbital	Topiramate	ethosuximide
phenytoin	Lamotrigine	valproate
carbamazepine	Felbamate	gabapentin
primidone	Rufinamide	clonazepam
oxcarbazepine	Clobazam	tiagabine
perampanel	Eslicarbazepine	levetiracetam
		zonisamide
		pregabalin
		vigabatrin
		lacosamide
		ezogabine

*Avoid concomitant use with the lowest dose oral contraceptive pills and additional non-hormonal forms of contraception should be used.

Table 2. Risk of major congenital malformations identified among infants who had been exposed to a specific AED monotherapy regimen during the first trimester and relative risk of MCMs compared to both unexposed and to lamotrigine groups: North America Pregnancy Registry 1997-2011^a

Antiepileptic Drug	Major Congenital Malformation ^b % (95% CI)	Relative Risk to Unexposed (95% CI)	Relative Risk to Lamotrigine (95% CI)
Unexposed ^c	1.1 (0.37-2.6)	Reference	
Lamotrigine	2.0 (1.4-2.8)	1.8 (0.7-4.6)	Reference
Carbamazepine	3.0 (2.1-4.2)	2.7 (1.0-7.0)	1.5 (0.9-2.5)
Phenytoin	2.9 (1.5-5.0)	2.6 (0.9-7.4)	1.5 (0.7-2.9)
Levetiracetam	2.4 (1.2-4.3)	2.2 (0.8-6.4)	1.2 (0.6-2.5)
Topiramate	4.2 (2.4-6.8)	3.8 (1.4-10.6)	2.2 (1.2-4.0)
Valproate	9.3 (6.4-13.0)	9.0 (3.4-23.3)	5.1 (3.0-8.5)
Phenobarbital	5.5 (2.8-9.7)	5.1 (1.8-14.9)	2.9 (1.4-5.8)
Oxcarbazepine	2.2 (0.6-5.5)	2.0 (0.5-7.4)	1.1 (0.4-3.2)
Gabapentin	0.7 (0.02-3.8)	0.6 (0.07-5.2)	0.3 (0.05-2.5)
Zonisamide	0 (0.0-3.3)	n/a	n/a
Clonazepam	3.1 (0.4-10.8)	2.8 (0.5-14.8)	1.6 (0.4-6.8)

CI = confidence interval; n/a = not applicable.

^a Adapted from Hernandez-Diaz, et al., Neurology 2012 (8).

^b Diagnosed during pregnancy or before 12 weeks after birth. Confirmed by review of medical records.

^c The unexposed internal comparison group were pregnant women not taking an antiepileptic drug who were recruited from among the friends and family members of the enrolled women taking an antiepileptic drug.

Table 3. Alterations of Antiepileptic Drug Clearance and/or Concentrations During Pregnancy: summary of Class I, II, and III studies (3, 19)

Antiepileptic Drug	Reported Increases in Clearance	Reported Decreases in Total Concentrations	Reported Changes in Free AED or Metabolites
Phenytoin	19 -150%	60-70%	Free phenytoin clearance increased in trimester 3 by 25%; free phenytoin concentration decreased by 16-40% in trimester 3
Carbamazepine	-11 to +27%	0%–12%	No change
Phenobarbital	60%	55%	Decrease in free phenobarbital concentration by 50%
Primidone	Inconsistent	Inconsistent	Decrease in derived PB concentrations, with lower PB/PRM ratios
Valproic acid	Increased by trimesters 2 and 3		No change in clearance of free VPA. Free fraction increased by trimesters 2 and 3
Ethosuximide	Inconsistent	Inconsistent	
Lamotrigine	65% - 230%, substantial interindividual variability		89% increase in clearance of free lamotrigine
Oxcarbazepine		Monohydroxy derivative & active moiety decreased by 36-61%	
Levetiracetam	243%	60% by trimester 3	

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