Management of epilepsy during pregnancy: an update

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***Abstract*:** The clinical management of women with epilepsy on antiepileptic drugs (AEDs) during pregnancy presents unique challenges. The goal of treatment is optimal seizure control with minimal *in utero* fetal exposure to AEDs in an effort to reduce the risk of structural and neurodevelopmental teratogenic effects. This paper reviews the following key issues pertaining to women with epilepsy during pregnancy: AED pharmacokinetics; clinical management of AEDs; seizure frequency; major congenital malformation; neurodevelopmental outcomes; perinatal complications; and breast feeding.

Keywords: antiepileptic drugs, breast feeding, epilepsy, neurocognitive development, perinatal outcomes, pregnancy, seizures, teratogenicity

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Introduction

In the United States, approximately 1.1 million women of childbearing age have epilepsy [Yerby, 2000]. Women with epilepsy (WWE) are advised to continue antiepileptic drugs (AEDs) during pregnancy to reduce maternal and fetal trauma associated with seizures. The goal is optimal seizure control with minimum fetal exposure to AEDs. Prenatal exposure to AEDs may be associated with major congenital malformations (MCM), intrauterine growth retardation, dysmorphic syndromes and deficits in neurocognitive development. These issues cause great concern in WWE who are thinking about having children. In the past, counseling WWE was challenging because little information was available about specific drugs and other commonly encountered situations. Several studies have provided valuable data on this topic and should become part of the working knowledge of all physicians caring for WWE. In this paper we review the most recent literature on key issues pertaining to WWE during pregnancy, particularly AED pharmacokinetics, clinical management of AEDs, seizure frequency, MCM, obstetrical risk during delivery, neurodevelopmental outcomes, perinatal complications and breast feeding.

A literature review was completed to identify recent studies pertaining to WWE and pregnancy. The PubMed database was searched with several key phrases, restricted to English articles, on 'management and treatment of women with epilepsy and pregnancy, pharmacokinetics of AEDs during pregnancy, AED management during pregnancy, side effects of AEDs during pregnancy, congenital malformations with embryonic and fetal exposure to AEDs, neurodevelopment of fetuses exposed to AEDs *in utero*, seizure frequency during pregnancy in WWE, effect of seizures on gestation, obstetrical risk, and breast-feeding and AEDs'. In addition, we searched bibliographies of review articles, original articles, established guidelines and book chapters on this topic.

Seizure frequency during pregnancy

In pregnant WWE, the cause for any increase in seizures is not clearly understood and is likely to be multifactorial. Pregnancy is associated with a number of physiological, endocrine and psychological changes, any or all of which might contribute to lowering the seizure threshold. Physiological changes during pregnancy alter the pharmacokinetics of AEDs, which may result in lower levels and seizure deterioration in WWE.

The best predictor of seizure frequency during pregnancy appears to be seizure frequency 1 year prior to pregnancy. In a study of WWE, 66.6% (n = 2521) of women were seizure-free during

their pregnancies [Battino *et al.* 2013]. Of the remaining 33.4% ($n = 1263$) of pregnant women that had seizures, 15.2% ($n = 576$) had generalized tonic–clonic convulsions (GTCC) and 18.2% ($n = 687$) had nonconvulsive seizures. In this cohort, seizure frequency was unchanged in 70.5% ($n = 2634$), 12.0% ($n = 448$) had a reduction in seizure frequency, and 15.8% ($n = 589$) had an increase in seizures. In the group that experienced increased seizures, 32% ($n = 189$) did so during the second trimester, 39% ($n = 229$) had an increase in the third trimester, and 29% ($n = 171$) had an increase in the second and third trimesters. There were 21 cases of status epilepticus, of which one resulted in perinatal death, and no maternal fatalities. Interestingly, worsening seizure control in the second and third trimester was more common in women taking lamotrigine (LTG) than those exposed to carbamazepine (CBZ) or valproic acid (VPA) [Battino *et al.* 2013]. Another study found seizures increased in 38.4% ($n = 44$) of patients during pregnancy despite increased AED doses; 44.3% ($n = 51$) had no change and 17.4% ($n = 20$) experienced a decrease in seizures for all trimesters compared with the preconception baseline [Reisinger *et al.* 2013]. Women with seizures 12 months prior to conception ($p < 0.001$), those with localization-related epilepsy ($p = 0.005$) and subjects on AED polytherapy were more likely to have seizure deterioration during their pregnancy [Reisinger *et al.* 2013]. Seizure deterioration may be attributed to multiple factors, including but not limited to noncompliance, reduction in plasma AED concentration and changes in AED metabolism, and possibly hormonal changes, sleep deprivation and psychosocial stress, although the latter factors have not been studied systematically.

Antiepileptic drug levels during pregnancy

During pregnancy, plasma AED concentrations may fluctuate due to physiologic changes in absorption, increases in renal clearance, altered hepatic clearance, increases in plasma volume distribution and hepatic enzymatic induction from female sex steroid hormones [Leppik and Rask, 1988]. These parameters vary depending on the AED that is utilized. In pregnancy, drug absorption may be altered due to decreased gastric tone and motility; however, this has not been proven in studies. Nausea and vomiting may affect drug ingestion, especially during the first trimester. Volume of distribution increases with weight gain and increases in plasma volume. An increase in total body water, results in a 40–50% increase in plasma volume [McAuley and Anderson, 2002]. Additionally, changes in hepatic drug metabolizing enzyme activity, blood flow and drug transporters may affect hepatic clearance of AEDs [Zhao *et al.* 2014]. These changes are important for AEDs metabolized by nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P450 reductase enzymes, uridine diphosphate glucose (UDP) glucuronosyltransferases enzymes and AEDs cleared by renal excretion. In general, increased clearance may affect AED concentrations and require dose adjustment to maintain pre pregnancy levels. A reduction in AED blood levels >35% from baseline pre pregnancy levels may result in increased seizures for some patients [Reisinger *et al.* 2013]. Ideally, target AED plasma concentrations should be determined for individual patients based on seizure history and therapeutic concentrations during preconception planning. It is a goal to maintain this target AED level throughout pregnancy in an effort to avoid seizures; AED doses may need to be modified as needed.

The AEDs that have the lowest rates of MCMs, such as LTG, levetiracetam (LEV) and oxcarbazepine (OXC), are often preferred for WWE who are contemplating pregnancy. These AEDs have increased clearance with changes in plasma drug levels during pregnancy and require close monitoring. Several studies have documented an increase in clearance of LTG and LEV during pregnancy [Tran *et al.* 2002; Reisinger *et al.* 2013; Petrenaite *et al.* 2009; Pennell *et al.* 2008]. An observational study of 53 pregnant women on LTG found the mean total LTG clearance increased by 94% in the third trimester compared with the nonpregnant baseline. Additionally, the investigators demonstrated, in the second trimester, that a LTG concentration <65% of the individual's baseline target concentration may predict seizures worsening [Pennell *et al.* 2008]. Another study also found that the mean peak clearance of LTG increased by 191% for 69 WWE on monotherapy LTG and 207% for 15 patients on monotherapy LEV during second trimester of pregnancy compared with the nonpregnant baseline [Reisinger *et al.* 2013]. Interestingly, in this same study it was noted that LTG clearance had marked variability with repeat singleton pregnancies, suggesting that the changes in LTG clearance observed in the first pregnancy may not be replicated in the second pregnancy for the same

patient [Reisinger *et al.* 2013]. Another study assessed the rate of oral clearance of LTG during pregnancy and postpartum period with a model-based approach; 60 pregnancies were studied and two subpopulations were identified. The majority of the women (77%) displayed a marked increase in LTG clearance whereas 23% had a minimal increase in LTG clearance from baseline [Polepally *et al.*, 2014]. The authors of this study suggest that genotypic variation may affect activity and induction of UGT1A4; however, more studies are needed to clarify this [Polepally *et al.*, 2014]. These studies highlight the importance of therapeutic drug monitoring during pregnancy to prevent seizure deterioration.

LEV also has increased clearance during pregnancy. In one study, LEV trough concentrations during the third trimester were 60% lower than baseline concentrations outside pregnancy in seven of 14 women, without dosage changes ($p < 0.001$) [Tomson and Battino 2007]. For 12 pregnancies, clearance of LEV was significantly higher during the third trimester, with an increase from 124.7 ± 57.9 (mean + standard deviation) liter/day at baseline to 427.3 ± 211.3 ($p < 0.0001$), an increase of 243%.

With regard to OXC, there is an increase in elimination of the OXC active metabolite 10-monohydroxy-10, 11-dihydro-carbamazepine (MHD) compared with pre pregnancy levels. A retrospective study of 13 patients on OXC monotherapy found an increase in elimination of MHD compared with pre pregnancy levels. The authors determined that the concentration to dose ratio (CDR) of MHD was decreased by 26.2% during the first trimester, by 36.5% during the second trimester and by 38.2% during the third trimester [Petrenaite *et al.* 2009]. This decrease in MHD was associated with seizure deterioration in nearly 64% of the patients. The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) study group reported that 58.5% of patient on OXC monotherapy had seizures during pregnancy or delivery. Additionally, in the EURAP study the use of OXC monotherapy was associated with a greater risk of convulsive seizures (OR: 5.4; 1.6-17.1) compared to other AED treatment regiments [EURAP, 2006].

Despite multiple factors that favor use of the second or third generation AEDs, many patients worldwide only have access to older AEDs. The pharmacokinetics of the older AEDs, such as CBZ, phenobarbital (PB), phenytoin (PHT) and VPA, during pregnancy have been reviewed in a few studies. Studies have documented a reduction in total plasma concentration of older AEDs during pregnancy, with a peak decrease in the third trimester [Leppik and Rask, 1988].

CBZ is available worldwide and is often used for WWE during pregnancy. Data on the pharmacokinetics of CBZ during pregnancy are mixed; some state that CBZ clearance increases throughout pregnancy and others state there is no significant difference. In one study, total and free CBZ and carbamazepine epoxide (CBZ-EPO) levels as well as seizure frequency were compared in 15 pregnancies (12 women) from nonpregnant baseline and each trimester. They found no significant change in the clearance of free and total CBZ and total and free CBZ-EPO throughout the pregnancy. Free CBZ concentrations decreased from baseline to first trimester ($p = 0.03$), but this was not sustained in the second and third trimester [Johnson *et al.* 2014]. Another small study ($n = 6$) showed similar results and treatment with CBZ monotherapy showed no increase in clearance throughout pregnancy [Reisinger *et al.* 2013]. In contrast to these findings, a study with a larger sample ($n = 35$) found that total CBZ did decrease during pregnancy in WWE. They found that CBZ decreased from baseline to third trimester by 23.9 μM to 21 μM [Tomson *et al.* 1994]. Certainly, the data on CBZ clearance are mixed and larger studies may help clarify CBZ pharmacokinetics during pregnancy.

Aside from CBZ, other commonly used AEDs worldwide are PHT, VPA and PB. These AEDs are not ideal during pregnancy, but they are often the only available AEDs in many developing countries. One study reported that total plasma concentrations of VPA, PHT and PB decreased significantly during pregnancy [Yerby *et al.* 1992]. Total PB concentration decreased by 55% in pregnancy, with the sharpest decrease noted in the first trimester, and unbound PB concentration decreases by 50%. Total PHT concentration decreased by 56–61%, with the sharpest decrease in the first trimester and the unbound concentration decreased by 18–33% in pregnancy [Yerby *et al.* 1992]. Another study noted a similar decrease in PHT [Tomson *et al.* 1994]. Compared with baseline, by the end of the third trimester the total PHT plasma concentration had decreased by 61% but the free PHT concentration had decreased by only 18%, and these concentration

decreases were not associated with an increase in seizure frequency [Tomson *et al.* 1994]. VPA concentrations were found to decrease by 39% throughout the pregnancy and unbound VPA levels to decrease by 22% [Yerby *et al.* 1992]. Multiple studies have identified a high risk of teratogenicity and neurocognitive delays with VPA. For some women with generalized epilepsy, VPA may be the only medication that controls their seizures. Some providers prefer VPA extended release formulation for better compliance and possible flat plasma concentration [Bialer *et al.* 2007]. However, there are no studies that provide data that support the use of VPA extended release *versus* immediate release formulation in WWE during pregnancy.

Studies [Pennell *et al.* 2008] highlight that therapeutic drug monitoring is effective with some AEDs in preventing seizure deterioration for WWE during pregnancy. Additionally, the AEDs that are frequently used during pregnancy, LTG and LEV, have a high clearance and concentrations should be monitored closely during pregnancy to prevent a decrease by more than 35% from preconception baseline and seizure deterioration. For the AEDs with high protein binding, clearance of total plasma AED and unbound fractions vary. Therapeutic drug monitoring is important during pregnancy in WWE [Patsalos *et al.* 2008]. Therapeutic drug monitoring of AED levels throughout pregnancy and maintaining target pre pregnancy AED levels may help prevent seizure deterioration during pregnancy.

Major congenital malformations: evidence from pregnancy registries

Fetal structural teratogenicity associated with *in utero* AED exposures has been investigated in several worldwide pregnancy registries, which are prospective observational studies. MCM are generally defined as 'structural abnormalities of surgical, medical, functional, or cosmetic importance' which occur during organogenesis in the first trimester [Tomson, 2012]. Some of the large prospective AED pregnancy registries are the North American Antiepileptic Drug Pregnancy Registry (NAAPR), the UK Epilepsy and Pregnancy Register, and EURAP. MCM outcomes associated with AEDs in these registries are listed in Table 1. Among these registries there are variations in methodology, making it difficult to compare across studies. Nonetheless, each registry provides valuable information on the association of AEDs and MCMs. Data from pregnancy registries have consistently shown, in monotherapy and polytherapy, that VPA is associated with the highest rates of fetal MCM, followed by PB and topiramate (TPM) [Hernandez-Diaz *et al.* 2012; Tomson *et al.* 2011]. Higher doses of VPA result in even higher MCM rates. *In utero* exposure to polytherapy AED has been associated with higher rates of fetal MCM compared with monotherapy AED in general, but more recent publications highlight that this is an oversimplification. We highlight each of the important findings in each registry in the following paragraphs.

NAAPR has assessed the risk of MCM identified by 12 weeks after birth with first trimester AED exposure. In 2012, it reported on 5667 women taking AED monotherapy for multiple reasons and compared them with 479 women who were unexposed to AED [Hernandez-Diaz *et al.* 2012]. The overall risk of MCM 12 weeks after birth with first trimester AED exposure was highest for VPA at 9.3% [95% confidence interval (CI) 6.4–13.0] (30 of 323), followed by PB at 5.5% [95% CI 2.8–9.7) (11 of 199), TPM at 4.2% (95% CI 2.4–6.8) (15 of 359), CBZ at 3.0% (95% CI 2.1–4.2) (31 of 1033) and PHT at 2.9% (95% CI 1.5–5.0) (12 of 416). Lowest MCM risk was noted for LTG at 2.0% (95% CI 1.4–2.8) (31 of 1562) and LEV at 2.4% (95% CI 1.2–4.3) (11 of 450). The group unexposed to AED had a 1.1% (95% CI 0.37–2.6) (5 of 442) risk of MCM. Higher doses of VPA >1500 mg per day were associated with an increased risk of MCM (>25%) compared with doses of <1500 mg per day, although risk was still high at approximately 10% for the group receiving 501–1500 mg per day. This dose-dependent relationship was not noted with other AEDs in the NAAPR. Additionally, VPA was associated with a higher risk of neural tube defects (1.2%, 95% CI 0.39–3.0) and hypospadias (3.1%, 95% CI 1.1–6.7). Cardiac defects were highest in both VPA (2.5%, 95% CI 0.12–4.6) and phenobarbital (2.5%, 95% CI 0.93–5.5). Oral cleft was 10 per 1000 in those fetuses exposed to PB, TPM and VPA compared with any reference population, in which oral cleft was 1 per 1000. In this patient population, oral cleft was noted to be the highest in PB (2%, 95% CI 0.64–4.8) followed by TPM (1.4%, 95% CI 0.51–3.1) and VPA (1.2%, 95% CI 0.39–3.0). The NAAPR results show that MCM risk was highest with VPA exposure and exaggerated further with higher doses.

Table 1. Pregnancy registries major congenital malformations (MCM) monotherapy antiepileptic drug (AED) exposure.

AED	NAAPR	UK Epilepsy and Pregnancy Register	EURAP
	n = 4899	*n* = 3607	*n* = 4540
	Hernandez-Diaz *et al.* [2012]	Morrow *et al.* [2006]	Tomson *et al.* [2011]
	MCM 3 months after birth	**MCM 6 weeks after birth**	**MCM 12 months after birth**
	% (95% CI) (n)	**% (95% CI) (n)**	**% (95% CI) (n); dose**
Lamotrigine	2% (1.4–2.8) (31)	3.2% (2.1–4.9) (21)	2.0% (1.19–3.24) (17); <300 mg /day 4.5% (2.77–6.87) (20); ⩾300 mg/day
Levetiracetam	2.4% (1.2–4.3) (11)	0% (0.0–14.9) (0)	–
Carbamazepine	3% (2.1–4.2) (31)	2.2% (1.4–3.4) (20)	3.4% (1.11–7.71) (5); <400 mg/day 5.3% (4.07–6.89) (56); ⩾400 mg/day to <1000 mg/day 8.7% (5.24–13.39) (18); ⩾1000 mg/day
Phenytoin	2.9% (1.5–5.0) (12)	3.7% (1.3–10.2) (3)	–
Valproic acid	9.3% (6.4–13.0) (30)	6.2% (4.6–8.2) (44)	5.6% (3.60–8.17) (24); <700 mg/day 10.4% (7.83–13.50) (50); ⩾700 mg/day to <1500 mg/day 24.2% (16.19–33.89) (24); ⩾1500 mg/day
Topiramate	4.2% (2.4–6.8) (15)	7.1% (2.0–22.6) (2)	–
Oxcarbazepine	2.2% (0.6–5.5) (4)	–	–
Gabapentin	0.7% (0.02–3.8) (1)	3.2% (0.6–16.2) (1)	–
Zonisamide	0% (0.0–3.3) (0)	–	–
Clonazepam	3.1% (0.4–10.8) (2)	–	–
Phenobarbital	5.5% (2.8–9.7) (11)	–	5.4% (2.51–10.04) (9); <150 mg/day 13.7% (5.70–26.26) (7); ⩾150 mg/day
Unexposed	1.1% (0.37–2.6) (5)	3.5% (1.8–6.8) (8)	–

CI, confidence interval; EURAP, International Registry of Antiepileptic Drugs and Pregnancy; NAAPR, North American Antiepileptic Drug Pregnancy Registry.

EURAP covers 42 countries and its objective is to determine the prevalence of MCM detected by 12 months after birth following *in utero* exposure to AEDs. It has reported on MCM rates following *in utero* exposure to monotherapy with CBZ, LTG, VPA or PB with analysis by dose-range intervals [Tomson *et al.* 2011]. Data for 3909 pregnancies exposed to four common AED monotherapies demonstrated an overall MCM rate of 6% (n = 230). The most important addition to our knowledge base was the finding that higher AED doses at the time of conception were associated with higher percentage of MCMs. LTG <300 mg per day had the lowest MCM rates at 2.0% (95% CI 1.19–3.24) (n = 17) and at ⩾300 per day MCM was 4.5% (95% CI 2.77–6.87) (n = 20). VPA had the highest MCM rate of 5.6% (95% CI 3.60–8.17 (n = 24) at <700 mg per day, 10.4% (95% CI 7.83–13.50) (n = 50) for ⩾700 to <1500 mg per day, and 24.2% (95%

CI 16.19–33.89) ($n = 24$) for ⩾1500 mg per day. CBZ had an MCM rate of 3.4% (95% CI 1.11–7.71) ($n = 5$) at <400 mg per day, 5.3% (95% CI 4.07–6.89) ($n = 56$) for ⩾400 to <1000 mg per day, and 8.7% (95% CI 5.24–13.39) ($n = 18$) for ⩾1000 per day. Lastly, PB had an MCM rate of 5.4% (95% CI 2.51–10.04) ($n = 9$) at <150 mg per day and 13.7% (95% CI 5.70–26.26) ($n = 7$) for ⩾150 mg per day. Cardiac defects were the most commonly reported MCM after exposure to these 4 AEDs; PB >150 mg per day had the highest percentage (8%) followed by VPA (7%). Parental history of MCM was associated with a four-fold greater risk in fetal MCM. Lastly, GTCC seizures in the first trimester were not associated with a higher risk for MCM.

The UK Epilepsy and Pregnancy Register is another prospective observational study that reports MCMs detected by 3 months of life in fetuses exposed to AEDs. The overall rate of MCM in fetuses exposed to AEDs *in utero* was 3.5% (95% CI 3–4%) [Campbell, 2014]. Updated results from the UK and Ireland Pregnancy Registry report the risk of MCM with VPA monotherapy is 6.7% (95% 95% CI 5.5–8.3) (82 of 1290), which carries a higher risk compared with LTG at 2.3% (95% 95% CI 1.8–3.1) (49 of 2198) and CBZ at 2.6% (95% 95% CI 1.9-3.5) (43 of 1718) [Morrow *et al.* 2006]. Moreover, this report highlights that high doses of LTG carry a lower risk of MCM compared with any dose of VPA. In this 2006 report, the overall risk for MCM with other monotherapy AEDs is LEV 0% (95% CI 0.0–14.9) (0 of 22), TPM 7.1% (95% CI 2.0–22.6) (2 of 28), GBP 3.2% (95% CI 0.6–16.2) (1 of 31) and PHT 3.7% (95% CI 1.3–10.2) (3 of 82) [Morrow *et al.* 2006]. The group unexposed to AED had a 3.5% (95% CI 1.8–6.8) (8 of 227) risk of MCM. MCM rates associated with LTG were dose dependent; a higher mean daily dose of LTG (352.4 mg *versus* 250.6 mg) was significantly associated with MCM. This dose response was not significant with VPA and CBZ.

The UK and Ireland Pregnancy Registry recently reported a low MCM risk associated with LEV, which is commonly used during pregnancy in WWE [Mawhinney *et al.* 2013]. In this study 671 pregnancies were followed, of which 304 were exposed to LEV monotherapy and 367 were exposed to LEV in combination with another AED. In the LEV monotherapy group, there were 0.70% (95% CI 0.19–2.51) MCM. The polytherapy group had overall MCM of 6.47% (95% CI 4.31–9.60), the LEV and LTG had the lowest rate of MCM at 1.77% (95% CI 0.49–6.22), followed by LEV and VPA at 6.90% (95% CI 1.91–21.96), and highest with LEV with CBZ at 9.38% (95% CI 4.37–18.98).

Recent reports demonstrate that the rates of MCMs for AED polytherapy vary substantially dependent on the type of *in utero* polytherapy exposure. Increased risk of MCM in infants exposed to AED polytherapy compared with monotherapy was highlighted in the UK registry reports [Morrow *et al.* 2006; Holmes *et al.* 2011]. The MCM rates were higher with polytherapy use at 6% (95% CI 4.5–8.0) compared with 3.7% (95% CI 3.4–5.0) in monotherapy, but MCM rates were highest when polytherapy regimens contained VPA [Morrow *et al.* 2006]. In the North American registry, infants exposed to LTG plus VPA had a 9.1% (95% CI 1.5–14.0) risk of MCM whereas it was 2.9% (95% CI 0.7–3.0) for LTG plus any other AEDs [Holmes *et al.* 2011]. The risk was higher at 15.4% (95% CI 2.0–16.5) for infants exposed to CBZ plus VPA, and 2.5% (95% CI 0.3–1.9) for CBZ plus any other AEDs [Holmes *et al.* 2011].

Management of epilepsy during pregnancy of WWE continues to be challenging, although recent studies provide high quality information to guide clinical decision making. Conclusions from these studies reinforce the following. First, VPA use should be avoided in women of childbearing age whenever possible. If a woman's seizures can only be controlled by VPA after all reasonable AED alternatives have failed, then VPA should be used at the lowest dosage possible to obtain reasonable seizure control. Attempts should be made to maintain VPA daily dosage <700 mg per day. Second, the number and dose of AEDs during the first trimester should be minimized to reduce the risk of MCM for the developing fetus, while maintaining seizure control based on the individual's epilepsy characteristics and target concentration. Third, LTG and LEV, in monotherapy and polytherapy use, are comparatively less teratogenic and are therefore considered favorable agents for the management of epilepsy during pregnancy. Lastly, therapeutic drug monitoring in some patients may help prevent seizure deterioration during pregnancy.

Obstetrical risk during delivery in WWE

Women with epilepsy may be at increased risk for obstetrical complications. A large, retrospective

cohort study of WWE (69,385) and women without epilepsy (WWoE) (20,449,532) found WWE are at higher obstetrical risk [MacDonald *et al.* 2015]. Women with epilepsy had more than a 10-fold increased risk of death [adjusted odds ratio (OR) 11.46, 95% CI 8.64–15.19], cesarean section (adjusted OR 1.40, 95% CI 1.38–1.42), preeclampsia (adjusted OR 1.59, 95% CI 1.54–1.63), seizures during preeclampsia (adjusted OR 5.18, 95% CI 4.65–5.77), induced labor (adjusted OR 1.14, 95% CI 1.12–1.16), severe postpartum hemorrhage (adjusted OR 1.76, 95% CI1.61–1.93), premature delivery (adjusted OR 1.54, 95% CI 1.50–1.57), experience of premature rupture of membranes (adjusted OR 1.07, 95% CI 1.03–1.11), developed chorioamnionitis (adjusted OR 1.17, 95% CI 1.11–1.23) and had longer hospital stay (more than 6 days) compared with WWoE [MacDonald *et al.* 2015].

A population-based study in Norway compared WWE with WWoE and found increased rates of mild preeclampsia (OR 1.3, 95% CI 1.1–1.5) and delivery before week 34 (OR 1.2, 95% CI 1.0–1.5) [Borthen *et al.* 2009]. Investigators in this study also gave consideration of WWE on AED and how this may affect delivery; they found that WWE on AED were at an increased risk of mild preeclampsia (OR 1.8, 95% CI 1.3–2.4), gestational hypertension (OR 1.5, 95% CI 1.0–2.2), vaginal bleeding late in pregnancy (OR 1.9, 95% CI 1.1–3.2) and delivery before 34 weeks of gestation (OR 1.5, 95% CI 1.1–2.0). It remains unclear if AED or epilepsy causes these complications.

Despite data supporting an increased obstetrical risk during delivery in WWE, some studies have not found a significant difference. For instance, one study reviewed singleton pregnancies in WWE (179) and singleton pregnancies in WWoE (24,778) and found no significant difference between the 2 groups in incidence of preeclampsia, preterm labor, rates of caesarean sections, perinatal mortality or low birth weight [Viinikainen *et al.* 2006].

WWE, especially those on AEDs, should be educated on possible obstetrical complications during delivery. Due to higher obstetrical complications, WWE should be monitored carefully during delivery. Additionally, WWE should be encouraged to follow with a doctor trained in obstetrics and gynecology whom may manage potential obstetrical complications during delivery.

Perinatal outcome in babies born to WWE

Neonates born to WWE taking AEDs are at higher risk for perinatal complications, such as low birth weight, small for gestational age (SGA), low Apgar scores, microcephaly, respiratory issues and admission to a neonatal care unit.

Several studies have noted that epilepsy and AEDs are associated with adverse perinatal outcomes [Pennell *et al.* 2012; Kilic *et al.* 2014; Artama *et al.* 2013]. In a large prospective observational study, a secondary analysis assessed the association between AEDs and 311 live births for perinatal complications, such as SGA, microcephaly and low Apgar scores [Pennell *et al.* 2012]. It was found that SGA was highest for neonates exposed to VPA (14.5%) and CBZ (12.9%). After controlling for confounding variables such as tobacco use, gestational diabetes and gestational age, SGA was more common for VPA > PHT, VPA > LTG and CBZ > PHT. The highest percentage of microcephaly was observed in 12-month-old infants exposed to CBZ (24%) and VPA (18%). The PHT and VPA groups were noted to have low (<7) 1-minute Apgar scores. Data from the EURAP registry, which followed 129 singleton pregnancies, found AED polytherapy exposure compared with monotherapy was associated with higher risk SGA [Rauchenzauner *et al.* 2013]. Additionally, GTCC during pregnancy was associated with shorter gestational age, prematurity and lower birth weight in primiparous women [Rauchenzauner *et al.* 2013].

Another retrospective population-based study assessed perinatal outcomes in WWE with singleton birth [Artama *et al.* 2013]. They analyzed perinatal outcomes in 4867 infants, including live births and stillbirths in WWE on AEDs, with comparisons to reference groups of WWoE and WWE not taking AEDs. Infants born to WWE have a slightly increased risk of perinatal complications compared with WWoE; infants of WWE were at higher risk for low 5-minute Apgar scores (adjusted odds ratio 1.19, 95% CI 1.04–1.36), requiring respiratory care (OR 2.10, 95% CI 1.57–2.81). In comparing WWE on AED to WWE not taking AED, they found an increased risk for treatment in a neonatal care unit (adjusted OR 1.48, 95% CI 1.21–1.82) for WWE on an AED. Women with epilepsy on AED polytherapy were at a 2–3 fold increased risk of several adverse outcomes. Additionally, there was a two-fold increase in risk of needing respiratory treatment in infants born to WWE on AED monotherapy

compared with infants born to WWoE. WWE on CBZ were noted to have an increased risk of preterm labor. The risk of low birth weight was also increased in WWE on AED, mainly CBZ, LEV and clonazepam (CLZ). Nearly a 6-fold risk in low birth weight was noted in the infants exposed to CLZ compared with WWoE and WWE with no AED; however, the sample size was only 164. Infants born to WWE that were exposed to VPA had an increased risk of low 1- and 5-minute Apgar scores [Artama *et al.* 2013].

A population-based study reviewed singleton births (679,762) from 1997 to 2008, of whom 2928 (0.4%) were exposed to AEDs [Kilic *et al.* 2014]. Children exposed to AEDs *in utero* were at higher risk for perinatal complications compared with children unexposed to AED. Children exposed to AEDs had an increased risk for preterm birth [adjusted risk ratio (aRR) 1.32], low birth weight (aRR 1.40) and SGA (aRR 1.21). Risk of preterm birth was increased in children exposed to CLZ, CBZ, OXC and LTG. Children exposed to CLZ, CBZ, VPA and LTG were at increased risk for low birth weight and SGA risk was increased for CLZ, CBZ, OXC, VPA and TPM. Exposure to primidone (PRM), CBZ and VPA was associated with low head circumference [Kilic *et al.* 2014].

Lastly, antenatal vitamin K is administered widely for women taking hepatic enzyme-inducing AED (EIAED) to avoid bleeding in the newborn. However, studies have not supported this practice. One larger study prospectively followed 662 pregnancies in WWE taking EIAED and 1324 pregnancies in WWoE. None of the mothers received vitamin K and they found no difference in the two groups. Bleeding was observed in 0.7% of the offspring exposed to maternal EIAED *versus* 0.4% in the control group [Kaaja *et al.* 2002]. The American Academy of Neurology (AAN) practice parameters for WWE state there is insufficient evidence to support or refute use of antenatal vitamin K to avoid new born hemorrhagic complications [Harden *et al.* 2009b].

These studies highlight that WWE and infants exposed to AEDs *in utero* are at higher risk for perinatal complications compared with WWoE [Artama *et al.* 2013]. In general, these data suggest that VPA is associated with SGA, lower 1-minute Apgar scores and microcephaly [Pennell *et al.* 2012]. Patients should be counseled on potential perinatal complications with AED use and VPA use should be avoided. Women who require treatment with VPA should be counseled on potential perinatal complications associated with VPA.

Infant AED exposure and neurocognitive development

Fetal exposure to AEDs is associated with a higher risk of neurodevelopmental deficits. Although this important topic has previously received little attention, cognitive development following *in utero* exposure to AEDs, occasionally called 'cognitive teratogenesis', has been highlighted in recent studies. This topic was rigorously addressed in the landmark Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study [Meador *et al.* 2013]; NEAD was a prospective observational study of cognitive development in children exposed *in utero* to VPA, LTG, CBZ or PHT monotherapy. A 6-year follow up of 224 children showed that intelligence quotient (IQ) at age 6 was lower in children exposed to VPA (mean 97) compared with CBZ (mean 105), LTG (mean 108) or PHT (mean 108) monotherapy. VPA exposure to doses higher than 1000 mg per day had a negative impact on verbal ability, nonverbal ability, executive function and memory in exposed children. Dose-dependent decline in cognitive development with *in utero* exposure was not remarkable with LTG, CBZ and PHT exposure. Significant independent predictors of a child's IQ were AED type and dose, older gestational age, use of periconceptional folate and higher maternal IQ. Children of mothers taking periconceptional folic acid had a higher Mean IQ (108) compared with 101 in the children of mothers who were not taking periconceptional folate. Once the women were seen clinically during pregnancy, virtually all of them were placed on supplemental folic acid.

In another prospective study, neurocognitive disorders were investigated in a cohort of children born to WWE on AED (n = 201); these children were followed until the age of 6 [Bromley *et al.* 2013]. Some of these children were included in the reports from the NEAD study. They found neurodevelopmental disorders were more frequently seen in children born to WWE (7.46%) compared with the control group (1.87%). Children exposed to VPA monotherapy (12.0%; aOR 6.05, 95% CI 1.65–24.53) or VPA in polytherapy (15.0%; aOR 9.9, 95% CI 1.82–49.40)

had an increased risk of neurodevelopmental disorders, and autism spectrum disorder (AED) was the most frequent diagnosis. This increase in risk was not identified with CBZ or LTG [Bromley *et al.* 2013]. Another recent study utilized the Childhood Autism Rating Scale (CARS) to determine risk of autism in 103 children with *in utero* exposure to AED; they determined higher doses of VPA use were associated with autistic traits [Wood *et al.* 2015]. The CARS scores were higher in the group exposed to VPA polytherapy (47%) and VPA in monotherapy (7.7%). The information from these studies can be used to educate WWE planning pregnancies or identify children exposed to AEDs that may have neurodevelopmental disorders.

Folate deficiency

Folate deficiencies have been associated with neural tube defects (NTD) in the general population. Supplementation with folic acid (0.36–4.0 mg) has been shown to reduce NTD risk by 60–86% in the general population [Yerby, 2003]. But this association is not clearly defined in WWE, especially those on AEDs. In one study, preconception use of folic acid (5 mg per day) in WWE resulted in no MCM, whereas no folic acid use was associated with 23% fetal abnormalities [Betts and Fox, 1999]. Some studies have found high dose folic acid (>5 mg per day) may be associated with enhanced vocabulary development, communicational skills and verbal comprehension at 18 months of age [Roth *et al.* 2011; Chatzi *et al.* 2012]. Low serum folate concentrations (<4.4mmol/l) have been associated as an independent risk factor for the occurrence of MCM in WWE [Kaaja *et al.* 2003]. In the NEAD study, children born to women taking periconception folate had a higher IQ; however, these data should be interpreted with caution since this information was ascertained retrospectively [Meador *et al.* 2013].

Most providers recommend folic acid use in WWE to prevent NTD. Dosing of folic acid is not clearly defined, but the ANN recommends at least 0.4 mg per day of folic acid prior to conception and during pregnancy in all women of child bearing age [Harden *et al.* 2009b]. Many experts recommend 1–5 mg per day, although there is now clear evidence to determine the optimal dose. More studies are needed to better define if folic acid prevents NTD or major congenital malformation in WWE taking AEDs.

Breast feeding and AEDs

Breast feeding newborns provide numerous benefits to maternal and infant well-being. However, many women have concerns about prolonging their baby's exposure to AEDs beyond gestation *via* breast milk. The benefits of breastfeeding *versus* the theoretical risk of drug exposure in the neonate should be discussed with the patient as well as her delivery team and pediatrician.

Infant exposure to AEDs in breast milk varies depending on multiple factors such as maternal plasma drug concentration, the milk/plasma ratio of the drug, the milk volume ingested by infant, and the absorption, metabolism and excretion of the drug in the infant. Even though an AED may appear in the breast milk, the degree of medication exposure to the newborn is still likely to be less than the degree of exposure during gestation. In general, AEDs with minimal protein binding and greater lipid solubility tend to distribute more readily into breast milk. Some AEDs such as PRM, LVT, GBP, LTG and TPM penetrate into breast milk in relatively high enough concentrations with the potential for clinical effects on the newborn [Harden *et al.* 2009a]. Other AEDs that are highly protein bound, such as VPA, PB, PHT and CBZ, do not to penetrate into breast milk in substantially high concentrations [Harden *et al.* 2009a]. Case series have not reported adverse effects on the newborn of AED exposure *via* breast milk, with the exception of some reports of sedation with the barbiturates and benzodiazepines. To minimize infant AED exposure, maternal AEDs should be kept to a low effective dose, and if signs of potential adverse reactions are noted (lethargy, poor feeding), infant serum concentrations can be monitored though is it not done routinely.

With recent data from breastfeeding women on AEDs and their children, we can state that the benefits of breastfeeding outweigh the risks to the infant. WWE taking AEDs should be encouraged to breast feed their baby if they choose, although many will supplement with 1–2 bottles per 24 hours to allow 1 period of more sustained sleep. The NEAD study investigated the effects of breastfeeding on child cognitive development (n = 195 mother–child pairs). They found there was no significant difference in the IQs of children tested at age 3 years old of children who were breast fed by mothers taking AEDs (CBZ, LTG, PHT or VPA monotherapy) compared with children who were not breastfed [Meador *et al.* 2010].

A follow-up 6-year study found similar results, but also found that breastfed children had a higher IQ (by 4 points) and increased verbal abilities (by 4 points) even after adjusting for confounding variables such as maternal IQ, AED dose and periconception folate use [Meador, 2014]. Another prospective population-based study found breastfed children of mothers taking AEDs had no adverse development at ages 6 and 16 months, and continuous breastfeeding was associated with less impaired development. Children who were continuously breastfed had favorable outcomes, despite maternal use of AEDs [Veiby *et al.* 2013]. Interesting, they found that continuous breastfeeding was less common for women taking AEDs. This highlights that some WWE on AEDs may feel reluctant to breastfeed their infants to prevent AED exposure *via* breast milk. It is important for providers to encourage and raise awareness that the benefits of breastfeeding outweigh the risk to the infant.

Conclusion

The clinical management of WWE on AEDs during pregnancy is challenging. The goal of treatment is optimal seizure control with minimal *in utero* fetal exposure to AEDs in an effort to reduce the risk of structural and neurodevelopmental teratogenic effects. Physiological changes during pregnancy alter the pharmacokinetics of AEDs, which may result in lower levels and seizure deterioration in some WWE, but therapeutic drug monitoring and AED dosage adjustment during pregnancy and postpartum can mitigate this. Patients should be carefully educated on potential major congenital malformation, neurodevelopmental outcomes, obstetrical risks, perinatal complications and breast feeding while on AEDs. It is important to monitor WWE during pregnancy, and despite multiple complexities in the care of WWE, it is important to highlight that the majority of WWE have healthy pregnancies.

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