ARTICLE

Fetal loss and malformations in the MONEAD study of pregnant women with epilepsy

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Abstract

Objective

To examine occurrence of severe adverse fetal outcomes (SAO), including fetal loss and major congenital malformations (MCMs), in pregnant women with epilepsy (PWWE) vs healthy pregnant women (HPW).

Methods

The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study is an NIH-funded, prospective, observational, multicenter investigation of pregnancy outcomes for both mother and child, which enrolled women December 2012 through January 2016.

Results

The 351 PWWE had 365 conceptions, and 105 HPW had 109 conceptions. SAOs occurred more often in PWWE (7.9%) vs HPW (1.9%) (p = 0.025) with odds ratio (OR) 4.45 (95% confidence intervals [CI] 1.04–19.01). There were no significant differences for fetal loss (2.8% vs 0%, p = 0.126) or MCMs (5.2% vs 1.9%, p = 0.185; OR 2.86, 95% CI 0.65–12.53) individually. No fetal losses in PWWE appeared to be related to acute seizures. Outcomes were not affected by periconceptional folate, unplanned/unwanted pregnancies, prior maternal pregnancy history, or antiepileptic drug (AED) blood levels, except for an AED level effect for fetal loss that appeared to be due to polytherapy. Combined maternal or paternal family history of MCM was marginally associated with increased SAOs (p = 0.046).

Conclusions

The findings provide additional information on risks of SAOs in PWWE, assessing effects of both AED levels and periconceptional folate. Group differences in average enrollment gestational age could have affected fetal loss results. Analyses are limited by small sample sizes as the MONEAD study was not powered for these secondary outcomes. The large majority of pregnancies in women with epilepsy do not have SOAs.

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Members of the MONEAD Investigator Group are listed at links.lww.com/WNL/B18.

Glossary

AED = antiepileptic drug; **CDC** = Centers for Disease Control and Prevention; **CI** = confidence interval; **%DDD** = percent defined daily dose; **EURAP** = European and International Registry of Antiepileptic Drugs and Pregnancy; **HPW** = healthy pregnant women; **MCM** = major congenital malformation; **MONEAD** = Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs; **NEAD** = Neurodevelopmental Effects of Antiepileptic Drugs; **OR** = odds ratio; **PWWE** = pregnant women with epilepsy; **SAO** = severe adverse fetal outcomes; **WWE** = women with epilepsy.

Pregnancy registries established in the 1990s have improved our understanding of the risks of fetal exposure to antiepileptic drugs (AEDs) for major congenital malformations (MCMs). Differential AED-induced teratogenic risks have been found, especially in regards to the higher risk for valproate.[1] However, these findings have altered prescription practices such that different AEDs are currently being preferentially used, while the data remain inadequate for many AEDs. Evidence on fetal risks during pregnancy is lacking for many AEDs, which leaves physicians without clear relatively low-risk choices beyond lamotrigine, levetiracetam, and carbamazepine.

The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study is a continuation of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study enrolling a new cohort. The primary goals of the MONEAD study are to delineate multiple maternal and child outcomes in pregnant women with epilepsy (PWWE) (e.g., seizure frequencies, obstetrical complications, neonatal complications, and neurodevelopmental outcomes in the children). In our prior NEAD cohort, we presented findings on early severe adverse fetal outcomes (SAO) including spontaneous fetal losses and MCMs.[2] Herein we present findings for the same outcomes from our MONEAD cohort of PWWE and a control group of healthy pregnant women (HPW) at 20 US tertiary epilepsy centers.

Methods

Design

The MONEAD study is an NIH-funded, prospective, observational, multicenter investigation of pregnancy outcomes for both PWWE and their children. The sample sizes were powered to assess primary outcomes (i.e., seizures, obstetric complications, depression, and neurodevelopmental outcomes). This publication describes the occurrence of SAOs (i.e., spontaneous fetal loss and MCMs) in offspring of PWWE vs HPW in the MONEAD study, all of which are secondary outcomes for the MONEAD study. Details of the MONEAD methodology have been published previously,[3] but are represented here in part to allow the reader to more easily interpret the present findings. Participants were enrolled from December 2012 through January 2016 at 20 US epilepsy centers that are specialized in the management of women with epilepsy (WWE) during childbearing years. The MONEAD sites are listed in appendix e-2 at links.lww.com/WNL/B18.

PWWE were recruited primarily from the clinical populations at the 20 MONEAD sites, but also via referral from obstetricians and other physicians, as well as PWWE self-referral. Inclusion criteria for PWWE were ages 14–45 years and ≤20 weeks gestational age. Exclusion criteria included expected IQ <70 or history of psychogenic nonepileptic spells, progressive cerebral disease, other major medical illness, or changes in AEDs during pregnancy prior to enrollment. Unlike the NEAD study, which enrolled only PWWE on the most common monotherapies, MONEAD was specifically designed to enroll all PWWE regardless of treatment regimen in order to obtain a representative sample of PWWE and their AED treatments. We also enrolled 2 control groups: HPW and nonpregnant WWE (NPWWE); enrollment criteria of these control groups were adjusted during the study to maintain relative similarity to the PWWE. In addition, the fathers and maternal relatives of children born to PWWE and HPW were also enrolled. Data were obtained from participants and their medical records.

Standard protocol approvals, registrations, and patient consents

This study was approved by the individual site institutional review boards and is registered on clinicaltrials.gov as NCT01730170. All adult participants signed informed consent prior to participation.

Outcome measures

For this report, the primary outcome was the occurrence of overall SAOs (i.e., spontaneous fetal losses and MCMs) in offspring of PWWE vs HPW. Secondary outcomes for this report are spontaneous fetal losses and MCMs analyzed separately as well as assessment of potential confounding factors.

Statistical analyses and outcome measures

Demographic variables for PWWE and HPW were summarized with counts and percentages for categorical variables and mean and SD for continuous variables. MCMs were adjudicated by a teratologist (R.F.) and neonatologist (L.V.M.) and assessed as those identified by 1 year post birth. Abnormalities related to a known genetic syndrome were excluded. The analysis population for spontaneous fetal loss and SAO were mother/child pairs with completed pregnancy (i.e., spontaneous fetal loss or live birth observed during the

study), and the analysis population for MCM analyses was all live births. PWWE and HPW who withdrew, were lost to follow-up prior to birth, or had elective abortions were excluded from all analyses (10 PWWE, 3 HPW). Frequency of fetal loss, MCM, and SAO were summarized with counts and percentages. Fisher exact test was used to compare frequencies of each outcome between HPW and PWWE, and odds ratios (ORs) for the SAOs and for MCMs in PWWE compared to HPW were computed using logistic regression models. Frequency of fetal loss, MCM, and SAO stratified by study group (PWWE, HPW) and the additional risk factors—periconceptional folate use, family history of prior malformations, and history of prior miscarriages—were also summarized with counts and percentages, and the Fisher exact test was used to compare outcome frequency for each risk factor within each study group. For history of prior miscarriages, only women with prior pregnancies were included in the analysis population. Periconceptional folate dose was analyzed as a categorical variable with 5 levels of daily dose (no folate, 0–0.4 mg, more than 0.4–1.0 mg, more than 1.0–4.0 mg, and more than 4.0 mg). Counts and percentages of SAO were summarized for each dose level and the Cochran-Armitage trend test was used to assess the effect of dose on SAO. The extent to which a fetal loss was attributed to the mother's seizures was collected during the study following a fetal loss as a 4-level variable ranging from not related to definitely related: these responses were used to assess said relationship.

To explore the effect of AED use on the outcomes for PWWE, frequency of fetal loss, MCMs, and SAOs stratified by AED use at enrollment grouped as monotherapy, polytherapy, and no AED were summarized with counts and percentages. Similar summaries were presented by specific individual AEDs or by combinations of AEDs for polytherapy. To compare the effect of dose across the various AEDs, a percent defined daily dose (%DDD) was calculated by dividing the mother's AED dose at enrollment by the WHO defined daily dose values[4,5] or derived from package inserts. The sum across the %DDD for each prescribed AED was used for mothers on polytherapy. Total AED concentrations were analyzed in the MONEAD Pharmacokinetics Core Laboratory to reduce interlaboratory variability. Blood samples were drawn during a clinic visit as convenience samples, and the time from last dose varied. AED blood levels measured at enrollment were standardized by calculating the % of concentrations within therapeutic ranges defined as the mother's AED blood level at enrollment divided by the calculated upper limit of suggested therapeutic ranges, mostly taken from published ranges,[4] and the remaining newer AEDs from clinical laboratory studies used by the Stanford clinics. The % therapeutic range for patients on polytherapy was calculated by summing the % suggested therapeutic range for each AED. Children of PWWE on AED at enrollment with missing blood levels were excluded from these analyses (30 children from 28 mothers). The %DDD and % therapeutic range was summarized with mean, SD, median, minimum, and maximum for mother/fetal pairs with and without fetal loss, MCM, and SAO. Separate logistic regression models for each outcome were used to calculate the OR and associated p value to assess if increased dose or AED levels were associated with higher odds of each outcome. Unadjusted models and models adjusted for monotherapy vs polytherapy were performed.

Data availability

All data included in these analyses will be shared as anonymized data via request from any qualified investigator.

Results

Demographics for the PWWE and HPW are given in table 1. The 351 PWWE enrolled had 337 singletons and 28 twins (14 pairs) for 365 conceptions. The 105 HPW enrolled had 101 singletons and 8 twins (4 pairs) for 109 conceptions. Mean ± SD gestational ages for conceptions at enrollment were 13.7 ± 4.6 weeks in PWWE and 15.4 ± 3.9 weeks in HPW. The types of epilepsy and the distributions of specific AEDs used in PWWE have been described previously,[3] but are described here briefly. Most PWWE (74%) were on monotherapy, and most had focal epilepsy (62%). The distributions of monotherapy, polytherapy, and no AED use in PWWE were comparable across different epilepsy types. Common AED monotherapy regimens were lamotrigine (42.1% of monotherapies) and levetiracetam (37.5%). Lamotrigine + levetiracetam (42.9% of polytherapies) was the most common AED polytherapy combination. Employment of other AEDs at the time of enrollment in the MONEAD study was much less frequent and variable across AEDs, especially for polytherapy. PWWE were not enrolled if AEDs were changed after onset of pregnancy and before enrollment. Thus AED use reflects exposure during the critical period in the first trimester.

PWWE enrolled at each center had a median of 13 (minimum = 3, maximum = 41). There was no significant difference in AED prescribing patterns related to year of enrollment (p = 0.7009, χ^2 test) or geographic region (p = 0.5622, χ^2 test).

Table 2 provides a summary of SAOs, fetal loss, and MCMs in PWWE and HPW as well as a summary by AED category for PWWE. SAOs occurred more often in PWWE (7.9%) than HPW (1.9%) (p = 0.025, Fisher exact test) with OR 4.45 (95% confidence interval [CI] 1.04–19.01). There were no statistical differences in MCMs, which occurred in 5.2% of PWWE and 1.9% of HPW (p = 0.185, Fisher exact test; OR 2.86, 95% CI 0.65–12.53). There were no statistical differences in fetal losses although no fetal losses occurred in HPW and there were 10 (2.8%) in PWWE (p = 0.126, Fisher exact test). In addition to the 10 spontaneous fetal losses (none reported with malformations), there were 2 elective abortions in PWWE: one was due to a serious medical event in the mother and the other was due to a genetic abnormality in the fetus. Of the 10 fetal losses, 9 were determined not to be related to mother's seizures, and 1 was assessed as possibly

Table 1 Demographics for pregnant women with epilepsy (PWWE) and healthy pregnant women (HPW) in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study

Group	PWWE	HPW
Total enrolled[a]	351	105
Mean age, y (SD)	31 (5)	30 (5)
Education, n (%)		
No college degree	104 (30)	32 (30)
College degree	159 (45)	39 (37)
Advanced degree	88 (25)	34 (32)
Mean IQ (SD)[b]	97 (13)	104 (13)
Race, n (%)		
White	295 (84)	75 (71)
Black or African American	25 (7)	17 (16)
Other	28 (8)	12 (11)
Participant declines to answer	3 (1)	1 (1)
Ethnicity, n (%)		
Hispanic or Latino	70 (20)	25 (24)
Non-Hispanic or non-Latino	281 (80)	80 (76)
AED category, n (%)		
AED monotherapy	261 (74)	—
AED polytherapy	75 (21)	—
Without AED	15 (4)	—
Seizure types[c]		
Generalized	110 (31)	—
Focal[d]	216 (62)	—
Unclassified	28 (8)	—
Pregnancies		
Singletons	337	101
Twins	28 (14 pairs)	8 (4 pairs)
Total conceptions	365	109

Abbreviation: AED = antiepileptic drug.
Some components of the demographics for PWWE were presented previously,[3] and are represented here to allow easy comparison to HPW.
[a] Eleven women terminated the study prior to birth visit (4 withdrew consent and 7 were lost to follow-up): 3 HPW (2.9%) and 8 PWWE (2.3%).
[b] Two PWWE had missing data for IQ score.
[c] Three patients reported multiple seizure types: 2 reported generalized and focal seizures and 1 reported generalized and unclassified seizures. Percentages represent the proportion of patients who have that seizure type and total may sum to more than 100%.
[d] Includes focal to bilateral tonic-clonic seizure.

related. Gestational ages (weeks) at the time of the 10 fetal losses in PWWE were 6, 7, 8, 9, 9, 10, 14, 16, 17, and 41 weeks. Thus, 9 were classified as spontaneous miscarriages and one as a fetal death. There were no MCMs reported in any of the spontaneous fetal losses or elective abortions. On average, PWWE were enrolled earlier in pregnancy (mean of 13.7 weeks gestation) than were HPW (mean of 15.4 weeks gestation).

Table 3 lists the observed individual MCMs by specific AEDs. Table 4 depicts SAOs, fetal losses, and MCMs as a function of AED blood levels. Overall, SAOs and MCMs were not related to AED blood levels. Post hoc analysis based on the unadjusted OR for fetal death (based on the rate of fetal death reported from the Centers for Disease Control and Prevention [CDC][6]) suggested that each unit increase in the % therapeutic range AED blood level is associated with a 6.00 increase in the odds of fetal death (95% CI 1.23–29.23). Although fetal loss was related to AED blood levels, after adjusting for AED category (monotherapy or polytherapy), the association was no longer significant, suggesting that the increase in risk is related to polytherapy. Mean AED blood levels and ranges for each AED are listed in table 5.

Overall SAOs, MCMs, and fetal losses were not related to AED dosages (tables 6 and 7). The occurrence of SAOs, fetal losses, and MCMs were not reduced by periconceptional folate or affected by folate dose. Similarly, these adverse events were not significantly affected by unplanned or unwanted pregnancies, maternal history of prior pregnancy with MCM or fetal loss, or maternal family history of MCM. However, maternal or paternal family history of MCM was marginally associated with an increase in SAO ($p = 0.046$).

Post hoc power analyses were performed to determine the minimum difference in fetal loss and MCMs that could be detected, using the observed sample sizes for PWWE and HPW. Calculations were performed at 80% power and a type 1 error rate of 0.05, using a Fisher exact test. For fetal loss, assuming a rate of 0.6% in the HPW group (based on CDC data[6]), the study had 80% power to detect a fetal loss rate of 6.7% or more in the PWWE group (higher than the observed 2.8% rate). For MCMs, assuming a 1.9% rate in the HPW group (based on the rate of MCM observed in the current study), the study had 80% power to detect a MCM rate of 9.7% or more in the PWWE group (higher than the observed 5.2% rate).

Discussion

The present findings provide new information on the risks of SAOs in PWWE. Although the risk of combined SAOs was increased in PWWE (7.9%) compared to HPW (1.9%), the large majority of children born to PWWE are normal. The SAOs were not affected by periconceptional folate, unplanned/unwanted pregnancies, prior maternal pregnancy history, AED type, or AED blood levels. The SAOs were 9.0% in the NEAD study vs 7.9% in MONEAD.[2] However, the NEAD study was composed of only AED monotherapies and

Table 2 Severe adverse outcomes (SAOs), fetal loss, and major congenital malformations (MCMs) by group and antiepileptic drug category

		SAO		Fetal loss		MCM		
Group	**Total conceptions**	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**	**Total live births**	**No.**	**% (95% CI)**
PWWE overall	355[a]	28	7.9 (5.3–11.2)	10	2.8 (1.4–5.1)	345	18	5.2 (3.1–8.1)
Monotherapy	266	19	7.1 (4.4–10.9)	5	1.9 (0.6–4.3)	261	14	5.4 (3.0–8.8)
LTG	113	8	7.1	3	2.7	110	5	4.5
LEV	99	7	7.1	2	2.0	97	5	5.2
CBZ	14	1	7.1	0	0.0	14	1	7.1
ZNS	13	1	7.7	0	0.0	13	1	7.7
TPM	6	1	16.7	0	0.0	6	1	16.7
Other monotherapy	21	1	4.8	0	0.0	21	1	4.8
Polytherapy	74	8	10.8 (4.8–20.2)	5	6.8 (2.2–15.1)	69	3	4.3 (0.9–12.2)
LTG + LEV	33	3	9.1	2	6.1	31	1	3.2
LEV + PHT	3	1	33.3	1	33.3	2	0	0.0
LTG + CLZ	2	1	50.0	0	0.0	2	1	50.0
LTG + ETX	2	1	50.0	1	50.0	1	0	0.0
Other polytherapy	34	2	5.9	1	2.9	33	1	3.0
None	15	1	6.7 (0.2–31.9)	0	0.0 (0.0–21.8)	15	1	6.7 (0.2–31.9)
HPW	106	2	1.9 (0.2–6.6)	0	0.0 (0.0–3.4)	106	2	1.9 (0.2–6.6)

Abbreviations: CBZ = carbamazepine; CI = confidence interval; CLZ = clonazepam; ETX = ethosuximide; HPW = healthy pregnant women; LEV = levetiracetam; LTG = lamotrigine; PHT = phenytoin; PWWE = pregnant women with epilepsy; TPM = topiramate; ZNS = zonisamide.
SAOs include fetal loss or MCM. Other monotherapies include CLZ, ETX, gabapentin, PHT, and phenobarbital. In other monotherapies, the single MCM was with gabapentin. In other polytherapies, the single fetal loss was with LTG + LEV + ZNS, and the single MCM was with LEV + phenobarbital.
[a] In addition to the 10 spontaneous fetal losses in PWWE, there were 2 elective abortions in PWWE and 8 losses to follow-up or withdrawal of consent.

included valproate, which has high risk and exhibited dose-dependent adverse effects for several outcomes. For comparison, if analyses are limited to monotherapy and exclude valproate, then the SAOs were 6.1% (95% CI 3.5–9.6) for NEAD vs 7.1% (95% CI 4.4–10.9) for MONEAD, which are comparable.

There were fetal losses in 2.8% of PWWE compared to none in HPW, but this difference was not statistically significant. The fetal losses in MONEAD are low, but average enrollment was earlier for PWWE than HPW, which could have affected results by providing more time to observe a fetal loss in the PWWE group, especially early in pregnancy when fetal loss is more common.[7] Had enrollment times between the groups been more similar (enrolling later in the PWWE group or earlier in the HPW group), it is likely that the difference in fetal loss would have been smaller. The rate of fetal losses was unaffected by periconceptional folate, unplanned/unwanted pregnancies, prior familial pregnancy history, or AED type. The risk of fetal loss appeared related to AED blood levels, but this effect was not significant adjusting for AED category (monotherapy or polytherapy), and thus appears related to polytherapy. It is possible that this difference was due to multiple AEDs or to disease or genetic differences in the polytherapy PWWE. Additional studies are needed to confirm this finding and differentiate underlying causes.

A systematic review found that WWE had increased risk of spontaneous miscarriage but not fetal death.[8] However, a multicenter prospective observational study enrolling WWE and healthy women prior to pregnancy and seeking conception found no increased rates of spontaneous miscarriages in WWE compared to the healthy controls.[9] In the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) study, rates of intrauterine death were similar across the different monotherapies (8.2%), but were higher with polytherapy (12.1%); the risk was also increased by the presence of MCMs in at least one of the parents.[6] The increased risk of fetal loss associated with polytherapy in EURAP is similar to MONEAD, and the risk from familial MCMs in EURAP is similar to this associated risk for SAOs in MONEAD.

The occurrence of MCMs did not differ significantly between PWWE (5.2%) and HPW (1.9%), but the sample size likely limited statistical power. The rate of malformations in

Table 3 Antiepileptic drugs (AEDs) and specific major congenital malformations

AED	Major congenital malformations
Monotherapy	
Carbamazepine	Hydronephrosis
Gabapentin	Paraesophageal jejunal herniation and inguinal hernia
Lamotrigine	Aortic coarctation
Lamotrigine	Cryptorchidism
Lamotrigine	Hydronephrosis
Lamotrigine	Morning glory syndrome
Lamotrigine	Pectus escavatum
Levetiracetam	Atrial septal defect
Levetiracetam	Buried penis syndrome
Levetiracetam	Cryptorchidism
Levetiracetam	Hypoplastic aortic valve
Levetiracetam	Ventricular septal defect
Topiramate	Ventricular septal defect
Zonisamide	Inguinal hernia and pinna malformation
Polytherapy	
Lamotrigine + clonazepam	Cardiomyopathy
Lamotrigine + levetiracetam	Microcephaly, myelomeningocele, and Chiari II malformation
Levetiracetam + phenobarbital	Bilateral inguinal hernia
No AED	
Child of PWWE on no AED	Undescended testicle
Child of HPW	Hydronephrosis and hydroureter
Child of HPW	Bicuspid aortic valve

Abbreviations: HPW = healthy pregnant woman; PWWE = pregnant woman with epilepsy.

the 15 PWWE not taking AEDs was similar to those taking AEDs; however, the sample size is very small, and larger studies have consistently reported lower risks for PWWE not taking AEDs.[10] In PWWE on AEDs, the risk of MCMs was not statistically related to periconceptional folate, unplanned/unwanted pregnancies, prior familial pregnancy history, AED type, or AED blood levels. The MCM rate of 5.2% in MONEAD is lower than NEAD overall (6.6%) but higher than NEAD without valproate (3.8%). Similarly, the MONEAD MCM rates are lower than those in reports for valproate, but are higher than other reports for lamotrigine and levetiracetam.[1,11–13] AED dose-dependent effects on MCMs have been reported for several AEDs,[14] and the lack of effects for AED levels in MONEAD are likely due to sample size.

Periconceptional folate reduces the risk of MCMs in the general population, especially in regards to spina bifida.[15,16] Recommendations from the American Academy of Neurology and the American Epilepsy Society in 2009 stated that the data are insufficient to show that folate is effective in reducing MCMs in PWWE, but noted that risk of MCMs in the offspring of PWWE is possibly decreased by folic acid supplementation based on 2 adequate Class III studies.[17] Another study reported reduced spontaneous abortion in pregnancies with folate supplementation.[18] In the present MONEAD study, there was no effect of periconceptional folate on overall SAOs, fetal loss, or MCMs; however, the use of folate in PWWE was high at 86%. Similarly, there was no effect of periconceptional folate on fetal loss or MCMs in the NEAD study,[2] and for MCMs in other studies of PWWE.[17,18] In contrast, periconceptional folate has been found to improve neurodevelopmental outcomes in women taking AEDs.[19–23] Combined maternal or paternal family history of MCM was marginally associated with an increase in SAO ($p = 0.046$). This finding is consistent with the known risk of family history of birth defects, but it can be affected by the method of collecting such histories.[24]

Strengths of the present study include the prospective design with detailed observational data collection including assessment of multiple confounding factors. The distribution of AEDs employed likely reflects current prescribing patterns for PWWE cared for in US epilepsy centers.[3] The MONEAD study is the first study to employ AED blood levels to assess the effects of AED exposure on pregnancy outcomes. Given the marked clearance changes occurring during pregnancy for several AEDs and uncertain clearance changes during pregnancy for other AEDs, it is common for doses to be adjusted during pregnancy. Therefore, the use of AED dose alone may misrepresent the actual drug exposure to the fetus, and AED levels are a more direct measure, thus AED levels were included in our analyses. The study was not randomized as there are ethical and practical restrictions to such studies in pregnancy. The main limitation of this study is the small sample size as the present analyses were a planned secondary outcome report, and not powered to be primary outcomes. As noted in our analyses, our study had 80% power to detect a fetal loss rate of 6.7% (higher than the observed 2.8% rate) or to detect an MCM rate of 9.7% (higher than the observed 5.2% rate). Thus the separate findings for fetal loss and for MCM have to be interpreted within this context.

The present findings add to the increasing information on pregnancy outcomes in PWWE. This study is the first to assess effects of both AED levels and periconceptional folate on pregnancy outcomes in PWWE. The present analyses on SAOs are limited by small sample sizes as this study was not powered for these secondary outcomes.

Table 4 Summary statistics for outcomes as function of antiepileptic drug (AED) blood levels (% therapeutic range)[a] for pregnant women with epilepsy on monotherapy and polytherapy

	Summary statistics				OR: raw		OR: adjusted for AED category	
	No.	Mean ± SD	Median	Min–max	OR (95% CI)	*p* Value[b]	OR (95% CI)	*p* Value[c]
SAOs (n = 310)								
Yes	22	0.53 ± 0.44	0.42	0.14–1.43	3.07 (0.98–9.65)	0.055	3.69 (0.76–17.91)	0.106
No	288	0.40 ± 0.31	0.31	0.01–1.52				
Fetal loss (n = 310)								
Yes	9	0.65 ± 0.45	0.50	0.16–1.42	6.00 (1.23–29.23)	0.027	4.04 (0.43–38.22)	0.223
No	301	0.40 ± 0.31	0.31	0.01–1.52				
MCMs (n = 301)								
Yes	13	0.45 ± 0.43	0.28	0.14–1.43	1.70 (0.34–8.52)	0.521	3.22 (0.39–26.26)	0.275
No	288	0.40 ± 0.31	0.31	0.01–1.52				

Abbreviations: CI = confidence interval; MCMs = major congenital malformations; OR = odds ratio; SAOs = severe adverse outcome (fetal loss or major congenital malformations).
Children of PWWE on AED at enrollment with missing blood levels excluded (30 children of 28 mothers).
[a] Based on mother's AED blood level at enrollment; % therapeutic range calculated as percent upper limit for therapeutic range; it was calculated by summing the % therapeutic range for each AED for patients on polytherapy.
[b] Unadjusted logistic regression model.
[c] Logistic regression model adjusted for AED category (monotherapy vs polytherapy).

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Disclosure

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Table 5 Antiepileptic drug (AED) blood levels[a] (ranges) for AED monotherapies in pregnant women with epilepsy[b]

	AED blood levels, μg/mL			
AED	**No.**	**Mean ± SD**	**Median**	**Min–max**
Lamotrigine	106	3.6 ± 2.0	3.2	0.3–9.9
Levetiracetam	92	13.9 ± 9.6	12.4	0.5–44.7
Carbamazepine	13	6.0 ± 1.5	6.1	2.5–8.6
Zonisamide	11	11.8 ± 6.2	10.5	3.8–23.8
Oxcarbazepine	9	10.6 ± 5.5	9.1	4.5–20.2
Topiramate	6	8.1 ± 4.5	7.5	3.2–15.6
Lacosamide	2	9.1 ± 7.8	9.1	3.6–14.6
Divalproex	1	24.7	24.7	24.7–24.7
Phenobarbital	1	10.3	10.3	10.3–10.3

[a] AED blood levels at time of enrollment.
[b] Excluding women who dropped out prior to birth/fetal loss or had elective abortion (n = 6).

Table 6 Percent defined daily dose (%DDD)[a] summary statistics by severe adverse outcomes (SAOs), fetal loss, and major congenital malformations (MCMs)

	Summary statistics				OR: raw		OR: adjusted for AED category	
	No.	Mean ± SD	Median	Min–max	OR (95% CI)	*p* Value[b]	OR (95% CI)	*p* Value[c]
SAOs (n = 340)								
Yes	27	1.84 ± 1.31	1.50	0.17–5.00	1.11 (0.81–1.52)	0.510	0.99 (0.65–1.53)	0.979
No	313	1.69 ± 1.16	1.33	0.21–6.57				
Fetal loss (n = 340)								
Yes	10	2.33 ± 1.32	2.00	0.83–4.67	1.43 (0.94–2.18)	0.091	1.11 (0.61–2.02)	0.738
No	330	1.68 ± 1.16	1.33	0.17–6.57				
MCMs (n = 330)								
Yes	17	1.55 ± 1.25	1.17	0.17–5.00	0.90 (0.57–1.42)	0.645	0.91 (0.50–1.64)	0.747
No	313	1.69 ± 1.16	1.33	0.21–6.57				

Abbreviations: CI = confidence interval; OR = odds ratio.
SAOs include fetal loss or MCM.
[a] %DDD is based on mother's antiepileptic drug dose at enrollment; for mothers on more than 1 antiepileptic drug at enrollment, %DDD equals the sum across the %DDD for all antiepileptic drugs.
[b] Unadjusted logistic regression model.
[c] Logistic regression model adjusted for antiepileptic drug category (monotherapy vs polytherapy).

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Table 7 Antiepileptic drug (AED) total daily dose (mg) at enrollment, pregnant women with epilepsy on monotherapy[a]

	AED dose, mg			
AED	**No.**	**Mean ± SD**	**Median**	**Min–max**
Lamotrigine	109	421 ± 222	400	100–1,400
Levetiracetam	95	1,912 ± 1,164	1,500	313[b]–7,000
Carbamazepine	14	800 ± 380	650	400–1,500
Zonisamide	13	385 ± 199	300	100–800
Oxcarbazepine	12	1,050 ± 438	900	600–1,800
Topiramate	6	271 ± 157	250	75–450
Lacosamide	2	550 ± 212	550	400–700
Divalproex	1	500	500	500–500
Felbamate	1	2,400	2,400	2,400–2,400
Gabapentin	1	300	300	300–300
Phenobarbital	1	50	50	50–50

[a] Excluding women who dropped out prior to birth/fetal loss or had elective abortion (n = 6).
[b] Participant was taking 250 mg/d alternating with 375 mg/d, giving an average of 313 mg/d.

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Appendix 1 Authors

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Appendix 1 *(continued)*

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Richard Finnell, PhD	Baylor College of Medicine, Houston, TX	Author	Contributed to study design, evaluated and adjudicated all malformations, reviewed and edited the manuscript for intellectual content

Appendix 2 Coinvestigators

Members of the MONEAD Investigator Group are listed at links.lww.com/WNL/B18

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