RESEARCH ARTICLE

Antiseizure Medication Dosing Strategy During Pregnancy and Early Postpartum in Women With Epilepsy in MONEAD

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Abstract

Background and Objectives

Antiseizure medications (ASMs) undergo marked pharmacokinetic alterations during pregnancy and postpartum. Suboptimal ASM management can lead to adverse maternal and child outcomes. However, there is scant literature to guide how to adjust ASM dosing. This study analyzed how ASMs were dosed in a large observational cohort study of pregnant women with epilepsy (PWWE) who had favorable seizure outcomes.

Methods

Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) was a prospective, observational cohort study that enrolled PWWE 2012–2016 across 20 US epilepsy centers. Inclusion criteria were PWWE, ages 14–45 years, and <20 weeks' gestational age. Seizures and ASM type(s) and doses were documented in a daily diary. Our analysis included ASM doses in pregnancy through early postpartum (6 weeks post-delivery). For each ASM, we analyzed percent participants who underwent ≥1 dose change in pregnancy and postpartum, time of first dose change after enrollment, time to subsequent changes, amount of each dose adjustment, and percent of conception dose at delivery and 6-week postpartum.

Results

A total of 299 participants (median 31 [range 17–46] years) were eligible for analysis. Median enrollment was 14-weeks gestation. Dose increases were made in 246/363 (67.8%) of ASMs during pregnancy beginning median 32 days post-enrollment; dose decreases were made within 6 weeks post-delivery for 171/357 (47.9%) of ASMs beginning median 3 days postpartum. For lamotrigine, 128/146 (87.7%) participants had doses increased, by 100 mg/d (median), reaching 191% of conception dose (mean) by delivery. Postpartum, 103/146 (70.5%) had dose tapers, by 100 mg/d (median), to 116% of conception dose (mean) by 6 weeks. For levetiracetam, 70/125 (56.0%) participants had doses increased, by 500 mg/d (median), reaching 177% of conception dose (mean) by delivery. Postpartum, 43/125 (34.4%) had dose tapers, by 500 mg/d (median), to 136% of conception dose (mean) by 6 weeks. For other ASMs, 10/14 had doses increased in pregnancy and 8/14 were tapered early postpartum.

Discussion

Previous MONEAD analyses showed no difference in seizure control between pregnant and nonpregnant women with epilepsy. We detail how ASMs were managed in pregnancy and early postpartum to achieve this favorable outcome. These findings can be useful for the management of PWWE. Limitations of this study include limited data in the first trimester, enrollment from epilepsy centers, and limited number of participants on a wider variety of ASMs.

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Glossary

ASM = antiseizure medication; **IQR** = interquartile range; **MONEAD** = Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs; **NPWWE** = non-pregnant women with epilepsy; **PWWE** = pregnant women with epilepsy.

Trial Registration Information

ClinicalTrials.gov Identifier: NCT01730170. Study Details | Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) | ClinicalTrials.gov. First submitted: November 9, 2012. First patient enrolled: December 19, 2012.

Introduction

Epilepsy affects more than 10 million individuals of childbearing potential worldwide,[1] and they often require individualized management during the reproductive years. During pregnancy, this involves balancing seizure control with potential adverse effects from antiseizure medications (ASMs) on the fetus. Generalized or focal-to-bilateral tonic-clonic seizures are especially dangerous to both the mother and developing fetus, with increased risk for mortality[2-4] and possibly lower verbal IQ in the children after 5 or more convulsive seizures during pregnancy.[5] Increased seizure frequency negatively affects quality of life,[6] and all seizure types that impair consciousness increase the risk for accidents and abdominal trauma with complications such as placental abruption.

Multiple physiologic and hormonal changes in pregnancy result in increased clearance for most ASMs. These changes include increased renal and hepatic blood flow, decreased protein binding, changes in cytochrome P450 enzymes, and rising estrogen levels which enhance glucuronidation, a significant metabolic pathway for lamotrigine, oxcarbazepine, and valproate.[7-10] Clearance increases in pregnancy are well-documented for phenobarbital, phenytoin,[10] lamotrigine,[10-15] levetiracetam,[16,17] oxcarbazepine,[18,19] zonisamide,[20] and topiramate.[21,22] These changes may happen very early in pregnancy and as early as 5 weeks' gestation for lamotrigine.[8] In contrast, studies of carbamazepine clearance demonstrate minimal increases for total total carbamazepine, with no significant changes for the active unbound (free) carbamazepine.[23]

Recommendations from practice guidelines state that clinicians should monitor ASM levels and adjust doses during pregnancy,[24-26] but there is minimal published data of how doses are specifically adjusted for any ASMs during pregnancy to maintain an individualized target drug level and adequate seizure control. Postpartum, there is a rapid reversal of physiologic[27] and hormonal[28,29] factors back to pre-pregnancy baselines. Increased ASM doses in pregnancy can cause supratherapeutic levels and toxicity if they are not tapered postpartum.[8,11,30,31] Some clinicians also may maintain an ASM dose that is slightly higher than the pre-pregnancy dose to account for postpartum seizure-provoking factors, such as sleep deprivation.[11] Published data on postpartum ASM dose changes are particularly scant.

The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study was a multicenter, prospective, observational cohort study, designed to evaluate maternal and child primary outcomes for pregnant women with epilepsy (PWWE), within an ASM pharmacokinetic framework to assess the level of maternal and fetal exposure to ASMs. We recognize that not all individuals of childbearing potential will identify as women, but we have chosen to use the term women in the remainder of the manuscript since inclusion criteria for the MONEAD study used the term woman from its onset in 2012. The 20 centers of enrollment were chosen for their established expertise in management of PWWE. Our prior publication reported increased clearance of several ASMs by calculating dose-normalized concentrations; we found that for a given total daily dose, ASM plasma concentrations would be decreased during pregnancy for lamotrigine, levetiracetam, oxcarbazepine, zonisamide, and lacosamide, with a trend for topiramate.[32] Total carbamazepine dose-normalized concentrations were minimally decreased, with no changes for unbound carbamazepine or carbamazepine-10,11-epoxide.[23]

Favorable maternal and child outcomes have been reported for the PWWE cohort in MONEAD. Compared with our control group of non-pregnant women with epilepsy (NPWWE), there was no difference in the percentage of women who had increased seizure frequency compared with their nonpregnant baseline, but ASM doses were increased more frequently in the PWWE cohort compared with the NPWWE cohort.[33] Moreover, children born to the PWWE cohort in MONEAD had excellent neurodevelopmental outcomes[34,35]; verbal index scores measured at age 6 years for the children born to the PWWE did not differ from scores in the children born to the control group of healthy pregnant women.[35] It is noteworthy, however, that approximately two-third of enrolled PWWE were on lamotrigine and/or levetiracetam. Data on ASM doses were collected in MONEAD for each participant from enrollment in pregnancy through delivery and 9 months postpartum, providing a unique opportunity to examine how epileptologists at the 20-enrolling

academic medical centers adjusted ASM doses to achieve the favorable maternal seizure and child neurodevelopmental outcomes. Additionally, given that most ASM dose changes after delivery in response to changing pharmacokinetics are made in the early postpartum period, we focused on ASM dose changes in the first 6-week postpartum.

Methods

MONEAD enrolled PWWE, NPWWE, and healthy pregnant participants, ages 14–45 years, at 20 epilepsy centers in the United States. This analysis is limited to the cohort of PWWE. Exclusion criteria included progressive cerebral disease, planned surgical intervention for epilepsy, history of functional seizures, substance use disorder in the previous year, >20 weeks' gestation, IQ < 70, or a change in the type of ASM before enrollment during pregnancy. Participants were recruited December 2012 through January 2016. Most of the participants were patients of the epilepsy clinics at the study sites. The ASM types and doses were determined by each participant's clinical team throughout the study.

Data consist of participant-level demographic information, medical and epilepsy history review from the participant and medical records, and prospective ASM doses for each day from enrollment through postpartum. We chose to use the self-reported dose at conception as an anchoring point. This was a retrospective detail the participants could readily recall and was verified by record review by the enrolling physician. The ASM and conception dose reflects the individual's epilepsy phenotype, including seizure types and drug responsiveness, as part of delivering a personalized medicine approach in pregnancy. After enrollment, participants inputted information in a daily electronic diary about ASM doses and regimen, adherence, and seizure occurrence by type. Site coordinators reviewed the electronic-diary entries with the participants at study visits, verified changes in drug type or dose, and entered any missing electronic-diary entries into a seizure log.

Statistical Analysis

ASM groups were defined by the participants taking a given medication at the time of conception (in monotherapy and polytherapy). For each ASM group, the median gestational week of enrollment, median number of days post-enrollment to first change, and the median days to subsequent changes were calculated, as well as the median change in dose in milligrams per day, and the mean percentage of conception-dose at delivery for participants who changed dose. Similar metrics were created for the early postpartum timelines but reported as days post-delivery and percent of conception dose at 6 weeks post-delivery. Medians are reported with interquartile range (IQR); mean percentages are reported with 95% CI.

Figures using locally estimated scatterplot smoothing regressions were created to display the change in ASM dose as compared with conception dose for each ASM group with >10 participants. Two panels were created for each ASM group, with a focus on participants with any dose changes: 1 for pregnancy and 1 for early postpartum. Participants with delivery <40 weeks had their doses at the time of delivery carried forward through gestational week 40 in the figures.

Standard Protocol Approvals, Registrations, and Patient Consents

The MONEAD was approved by the institutional review board at each study site. All participants provided written informed consent to participate in this research study. Although MONEAD was a prospective cohort study and not a clinical trial, the study was registered on ClinicalTrials.gov Identifier: NCT01730170.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator whose proposed use of the data has been approved and with a signed data access agreement.

Results

Participants

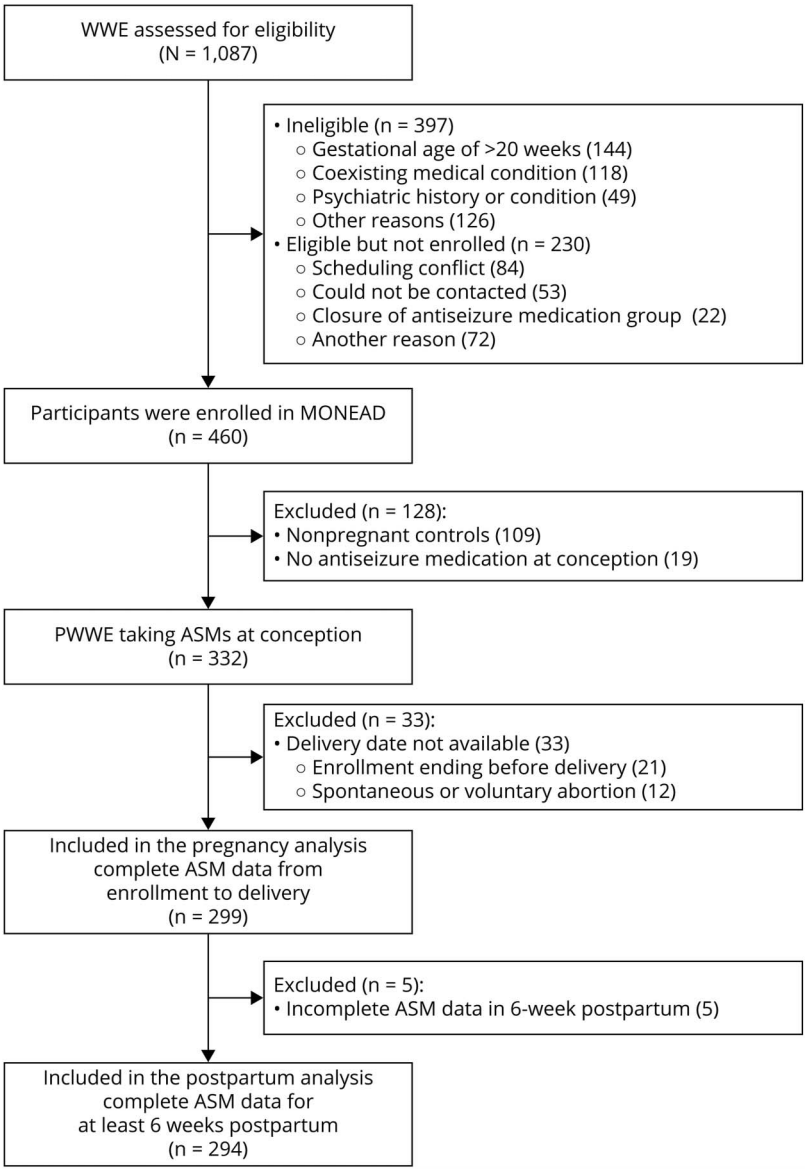
After applying inclusion and exclusion criteria, we analyzed data from 299 participants from April to December 2024. In total, the 299 participants received prescriptions for 363 ASMs (accounting for 61 participants on polytherapy with 2 or more ASMs) for at least 7 days after conception (Figure 1). Lamotrigine was prescribed to 146/299 (48.8%) participants and levetiracetam prescribed to 125/299 (41.8%) of the PWWE analyzed. Table 1 includes the number of participants, demographic data, and seizure types sorted by ASM.

ASM Changes in Pregnancy After Enrollment

Of the 363 ASM exposures in all participants at the time of conception, 246 (67.8%) underwent dose changes during pregnancy. The median (IQR) time to enrollment for all participants was 14 (11–18) gestational weeks, with the time to first dose change occurring a median (IQR) of 32 (7–78) days post-enrollment. Details by ASM are in Table 2.

The timeline of dose changes among participants on lamotrigine who changed dose at least once during pregnancy (87.7%, 128/146) is illustrated in Figure 2A. Median (IQR) time to the first dose change was 32 (6–75) days post-enrollment, with 35 (17–60) days between the first and second dose change and 26 (13–52) days between the second and third dose change. Sixty-six percent had 2 or more changes, and 46.6% had 3 or more changes, with a maximum of 11 dose changes for 1 participant. Doses were increased by a median of 100 mg/d each time, with an IQR of 75–200 mg for the first change and 50–100 mg for the second and third changes. Notably, in the participant with 11 dose changes,

Figure 1 Enrollment and Outcomes Consort Diagram



PWWE were excluded from analysis if there was missing ASM data at conception or a missing delivery date. ASM = antiseizure medication; MONEAD = Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs; PWWE = pregnant women with epilepsy; WWE = women with epilepsy.

approximately half were by 50 mg/d in 5–7-day intervals. In participants who changed dose, the mean (95% CI) dose at delivery was 191% (175%–206%) of the conception dose.

The timeline of dose changes among participants on levetiracetam who changed dose at least once during pregnancy (56%, 70/125) is illustrated in Figure 3A. Median (IQR) time to the first dose change was 47 (17–94) days post-enrollment, with 47 (28–64) days between the first and second dose change and 37 (14–54) days between the second and third dose change. Thirty percent had 2 or more changes, and 17% had 3 or more changes, with a maximum of 7 dose changes for 1 participant. Doses were increased by median 500 mg/d for each of the first 3 changes. The IQR for the first change was 500–500 mg/d, for the second change was 406–500 mg/d, and for the third change was 250–500 mg/d. The mean (95% CI) dose at delivery was 177% (155%–199%) of the conception dose.

The timeline of dose changes among participants on oxcarbazepine who changed dose at least once during pregnancy (67%, 12/18) is illustrated in Figure 4A. Median (IQR) time to the first dose change was 64 (49–93) days after enrollment. Six participants (33%) had 2 or more changes. The median (IQR) time between the first and second change was 52 (41–71) days. Doses were increased by a median of 300 mg/d for each of the first 2 changes, with an IQR of 262–375 mg/d for the first change and 187–300 mg/d for the second change. The mean (95% CI) dose at delivery was 153% (124%–182%) of the conception dose.

Table 1 Demographic Characteristics of Pregnant Women With Antiseizure Medication Data From Enrollment to Delivery

Cohort variable	CBZ	CLZ	ESM	FBM	GBP	LCM	LTG	LEV	LZP	OXC	PHB	PHT	PGB	TPM	VPA	ZNS	Polytherapy	All Participants
Pregnant women with epilepsy, n	17	2	2	2	3	7	146	125	3	18	3	2	1	12	3	17	61	299
Age, y, median (range)	30 (21–40)	33 (27–39)	26.5 (23–30)	26.5 (24–29)	32 (26–33)	34 (30–41)	32 (19–43)	31 (17–46)	27 (24–39)	29.5 (19–35)	37 (31–39)	27 (24–30)	34 (34–34)	27.5 (23–39)	32 (27–32)	28 (19–41)	30 (19–41)	31 (17–46)
Race, n (%)																		
Asian	3 (17.6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	4 (2.7)	3 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	0 (0)	1 (1.6)	11 (3.7)
Black or African American	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (6.2)	7 (5.6)	1 (33.3)	2 (11.1)	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (5.9)	3 (4.9)	17 (5.7)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
White	11 (64.7)	2 (100)	2 (100)	1 (50)	2 (66.7)	6 (85.7)	129 (88.4)	108 (86.4)	2 (66.7)	16 (88.9)	3 (100)	2 (100)	1 (100)	10 (83.3)	3 (100)	15 (88.2)	54 (88.5)	257 (86)
Multiracial	1 (5.9)	0 (0)	0 (0)	1 (50)	1 (33.3)	0 (0)	2 (1.4)	5 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.9)	2 (3.3)	9 (3)
Other/unknown	2 (11.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.4)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.6)	4 (1.3)
Ethnicity, n (%)																		
Hispanic or Latino	4 (23.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	20 (13.7)	37 (29.6)	0 (0)	4 (22.2)	1 (33.3)	1 (50)	0 (0)	1 (8.3)	0 (0)	2 (11.8)	14 (23)	57 (19.1)
Non-Hispanic or Non-Latino	13 (76.5)	2 (100)	2 (100)	2 (100)	3 (100)	6 (85.7)	126 (86.3)	88 (70.4)	3 (100)	14 (77.8)	2 (66.7)	1 (50)	1 (100)	11 (91.7)	3 (100)	15 (88.2)	47 (77)	242 (80.9)
Seizure type, n (%)																		
Focal	14 (82.4)	1 (50)	0 (0)	1 (50)	2 (66.7)	5 (71.4)	92 (63)	68 (54.4)	2 (66.7)	16 (88.9)	3 (100)	2 (100)	1 (100)	7 (58.3)	0 (0)	2 (11.8)	34 (55.7)	179 (59.9)
Generalized	0 (0)	1 (50)	2 (100)	1 (50)	1 (33.3)	2 (28.6)	43 (29.5)	49 (39.2)	1 (33.3)	2 (11.1)	0 (0)	0 (0)	0 (0)	4 (33.3)	3 (100)	15 (88.2)	25 (41)	99 (33.1)
Generalized and focal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	0 (0)	0 (0)	2 (0.7)
Generalized and unclassified	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Unclassified	3 (17.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (6.8)	7 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.3)	18 (6)

Abbreviations: CBZ = carbamazepine; CLZ = clonazepam; ESM = ethosuximide; FBM = felbamate; GBP = gabapentin; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; LZP = lorazepam; OXC = oxcarbazepine; PHB = phenobarbital; PHT = phenytoin; PGB = pregabalin; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.

Table 2 Summary of Antiseizure Medication Dose Changes in Pregnancy After Enrollment and 6 Weeks Postpartum

	LTG	LEV	OXC	CBZ	ZNS	TPM	LCM	VPA	PHB	LZP	GBP	PHT	CLZ	ESM	FBM	PGB
N at enrollment	146	125	18	17	17	12	7	3	3	3	3	2	2	2	2	1
Pregnancy																
≥1 change in pregnancy, n (%)	128 (88)	70 (56)	12 (67)	8 (47)	12 (71)	6 (50)	2 (29)	2 (67)	1 (33)	0 (0)	1 (33)	1 (50)	0 (0)	1 (50)	2 (100)	0 (0)
Gestational weeks at enrollment, median (IQR)[a]	14 (9 to 17)	14 (11 to 19)	12 (9 to 16)	17 (12 to 19)	14 (12 to 20)	14 (11 to 17)	13 (11 to 18)	6 (5 to 8)	17 (14 to 19)	13 (12 to 15)	14 (14 to 18)	9 (7 to 11)	18 (17 to 20)	12 (11 to 13)	13 (12 to 14)	13 (12 to 13)
Days after enrollment to first change, median (IQR)	32 (6 to 75)	47 (17 to 94)	64 (49 to 93)	31 (13 to 56)	63 (26 to 77)	63 (36 to 83)	91 (74 to 107)	17 (8 to 25)	72[c]	NA	80[c]	78[c]	NA	71[c]	92 (84 to 99)	NA
Days from first to second change, median (IQR)	35 (17 to 60)	47 (28 to 64)	52 (41 to 71)	46 (39 to 70)	65 (39 to 110)	36 (28 to 43)	32[c]	NA	NA	NA	30[c]	NA	NA	NA	20[c]	NA
Days from second to third change, median (IQR)	26 (13 to 52)	37 (14 to 54)	40 (35 to 45)	7 (6 to 8)	99[c]	48 (27 to 68)	45[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA
First dose change, mg, median (IQR)	100 (75 to 200)	500 (500 to 500)	300 (262 to 375)	200 (100 to 325)	100 (100 to 113)	50 (50 to 88)	38 (6 to 69)	−63 (−157 to 32)	10[c]	NA	400[c]	50[c]	NA	250[c]	450 (375 to 525)	NA
Second dose changes, mg, median (IQR)	100 (50 to 100)	500 (406 to 500)	300 (187 to 300)	100 (−200 to 200)	100 (100 to 100)	−75 (−88 to −62)	25[c]	NA	NA	NA	400[c]	NA	NA	NA	300[c]	NA
Third dose changes, mg, median (IQR)	100 (50 to 100)	500 (250 to 500)	300 (225 to 300)	−50 (−125 to 25)	−100[c]	−25 (−63 to 13)	75[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mean % of conception dose at delivery (95% CI)[b]	191 (175 to 206)	177 (155 to 199)	153 (124 to 182)	123 (111 to 135)	138 (120 to 156)	144 (119 to 169)	127 (113 to 140)	108 (27 to 190)	120[c]	NA	133[c]	113[c]	NA	120[c]	122 (91 to 153)	NA
6 wk postpartum																
≥1 change within 6 wk postpartum, n (%)	103 (71)	43 (34)	7 (39)	4 (24)	4 (24)	3 (25)	3 (43)	1 (33)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	1 (50)	1 (50)	0 (0)
Days after delivery to first change, median (IQR)	2 (1 to 7)	3 (1 to 8)	7 (6 to 11)	4 (1 to 12)	7 (4 to 13)	10 (9 to 14)	2 (2 to 13)	18[c]	NA	NA	1[c]	NA	NA	8[c]	16[c]	NA
Days from first to second change, median (IQR)	4 (4 to 7)	6 (4 to 7)	5 (5 to 26)	7[c]	7 (5 to 8)	NA	4[c]	NA	NA	NA	6[c]	NA	NA	NA	NA	NA
Days from second to third change, median (IQR)	4 (3 to 5)	3 (3 to 4)	5 (5 to 5)	7[c]	24[c]	NA	3[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA
First dose changes, mg, median (IQR)	−100 (−200 to −100)	−500 (−625 to −250)	−300 (−450 to −300)	−150 (−225 to −100)	−100 (−100 to −87)	−50 (−75 to 0)	−50 (−50 to 25)	250[c]	NA	NA	−400[c]	NA	NA	−250[c]	−300[c]	NA
Second dose changes, mg, median (IQR)	−100 (−100 to −50)	−500 (−500 to −343)	−300 (−300 to 300)	−100[c]	−75 (−88 to −62)	NA	−50[c]	NA	NA	NA	−400[c]	NA	NA	NA	NA	NA
Third dose changes, mg, median (IQR)	−100 (−100 to −50)	−375 (−500 to −250)	−225 (−263 to −187)	−100[c]	−50[c]	NA	−25[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA

Continued

Table 2 Summary of Antiseizure Medication Dose Changes in Pregnancy After Enrollment and 6 Weeks Postpartum *(continued)*

	LTG	LEV	OXC	CBZ	ZNS	TPM	LCM	VPA	PHB	LZP	GBP	PHT	CLZ	ESM	FBM	PGB
Mean % of conception dose at 6 wk postpartum (95% CI)[b]	116 (107 to 124)	136 (115 to 158)	129 (101 to 158)	100 (88 to 112)	113 (88 to 137)	128 (99 to 157)	110 (86 to 133)	100[c]	NA	NA	100[c]	NA	NA	100[c]	100[c]	NA

Abbreviations: CBZ = carbamazepine; CLZ = clonazepam; ESM = ethosuximide; FBM = felbamate; GBP = gabapentin; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; LZP = lorazepam; NA = not applicable; OXC = oxcarbazepine; PGB = pregabalin; PHB = phenobarbital; PHT = phenytoin; TPM = topiramate; VPA = valproic acid; ZNS = zonisamide.
[a] Time to enrollment among all participants on a medication.
[b] Mean % of conception dose among participants with dose changes in pregnancy or within 6 weeks postpartum, respectively.
[c] N of 1.

The timeline of dose changes among participants on carbamazepine who changed dose at least once during pregnancy (47%, 8/17) is illustrated in Figure 5A. Median (IQR) time to first dose change was 31 (13–56) days post-enrollment. Five participants (29%) had 2 or more changes.

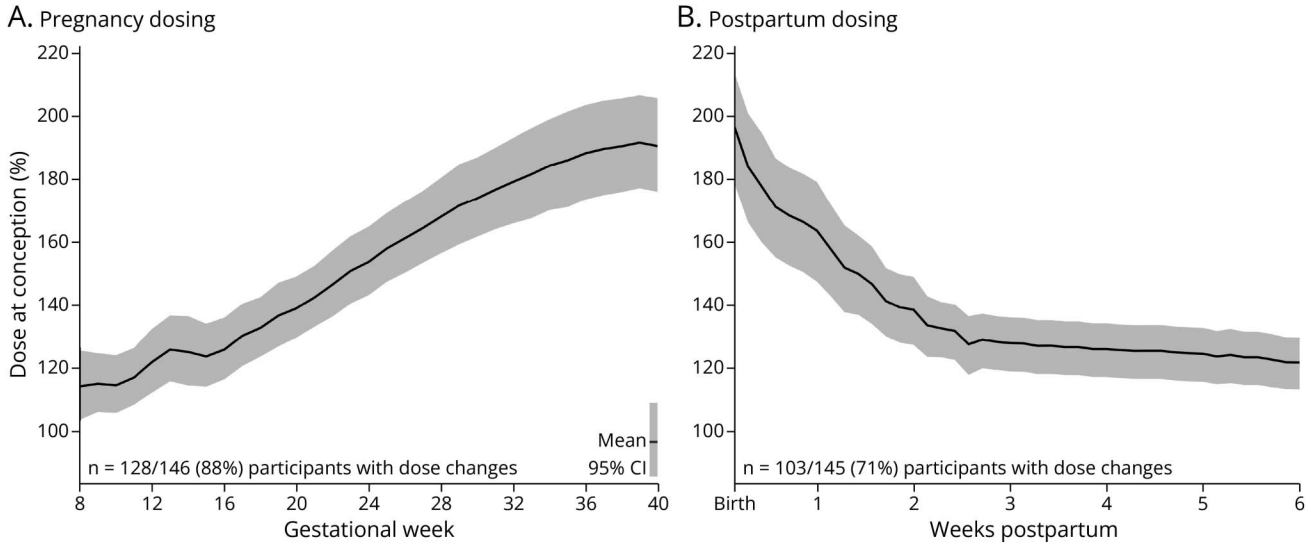
Oxcarbazepine doses were increased by median (IQR) 200 (100–325) mg/d for the first dose change and 100 (−200 to 200) mg/d for the second dose change. The mean (95% CI) dose at delivery was 123% (111%–135%) of the conception dose.

For participants on zonisamide, 71% (12/17) changed dose at least once during pregnancy, with 24% (4/17) with 2 or more changes. Median (IQR) time to first dose change was 63 (26–77) days after enrollment. The median (IQR) number of days between the first and second change was 65 (39–110) days. Doses were increased by a median of 100 mg/d for the first and second changes, with an IQR of 100–113 mg for the first dose change and 100–100 mg for the second change. The mean (95% CI) dose at delivery was 138% (120%–156%) of the conception dose.

For participants on topiramate, 50% (6/12) changed dose at least once during pregnancy, and 17% (2/12) had 2 or more changes. Median (IQR) time to first dose change was 63 (36–83) days after enrollment. Doses were increased by median (IQR) of 50 (50–88) mg/d for the first dose-change but followed by a decrease of 75 (62–88) mg/d for the second dose change. The mean (95% CI) dose at delivery was 144% (119%–169%) of the conception dose.

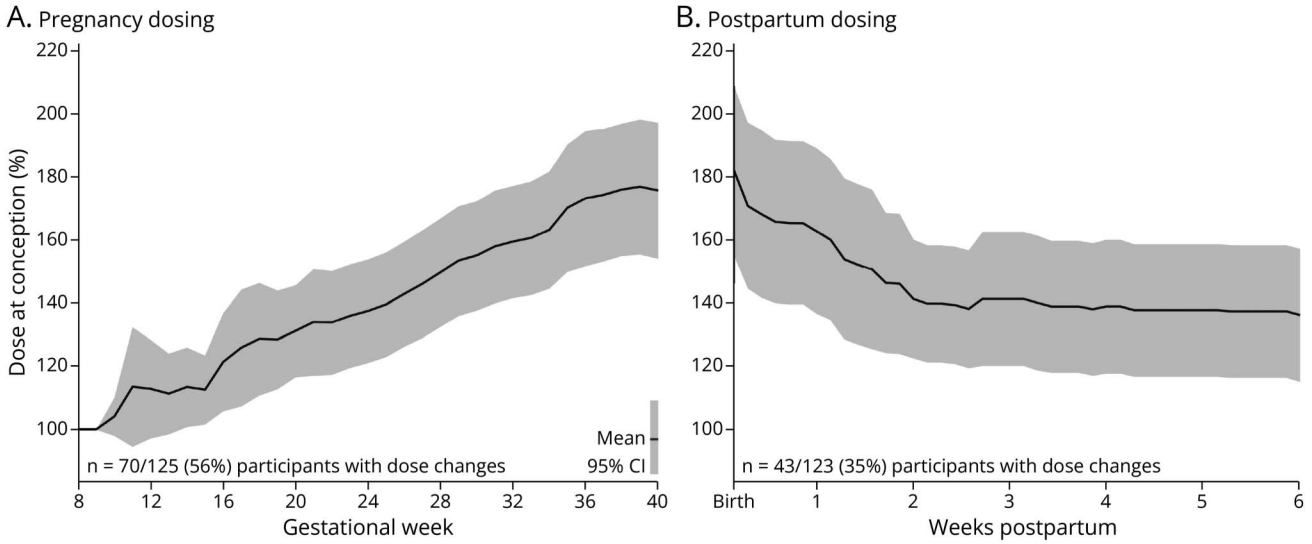
Additional details about pregnancy ASM dose changes are in Table 2. For zonisamide and topiramate, which were the other

Figure 2 Lamotrigine Dosing in Pregnancy and Postpartum



Locally estimated scatterplot smoothing regressions showing the percent of conception dose over time among participants with lamotrigine dose changes in pregnancy after enrollment (panel A, 128/146 [87.7%] participants) and first 6-week postpartum (panel B, 103/146 [70.5%] participants). The solid line represents the mean, and the shading represents the 95% CI. Participants who delivered at or after 34 weeks had their doses at delivery carried forward through gestational week 40 in panel A.

Figure 3 Levetiracetam Dosing in Pregnancy and Postpartum



Locally estimated scatterplot smoothing regressions showing the percent of conception dose over time among participants with levetiracetam dose changes in pregnancy after enrollment (panel A, 70/125 [56%] participants) and first 6-week postpartum (panel B, 43/123 [35%] participants). The solid line represents the mean and the gray shading represents the 95% CI. Participants who delivered at or after 34 weeks had their doses at delivery carried forward through gestational week 40 in panel A.

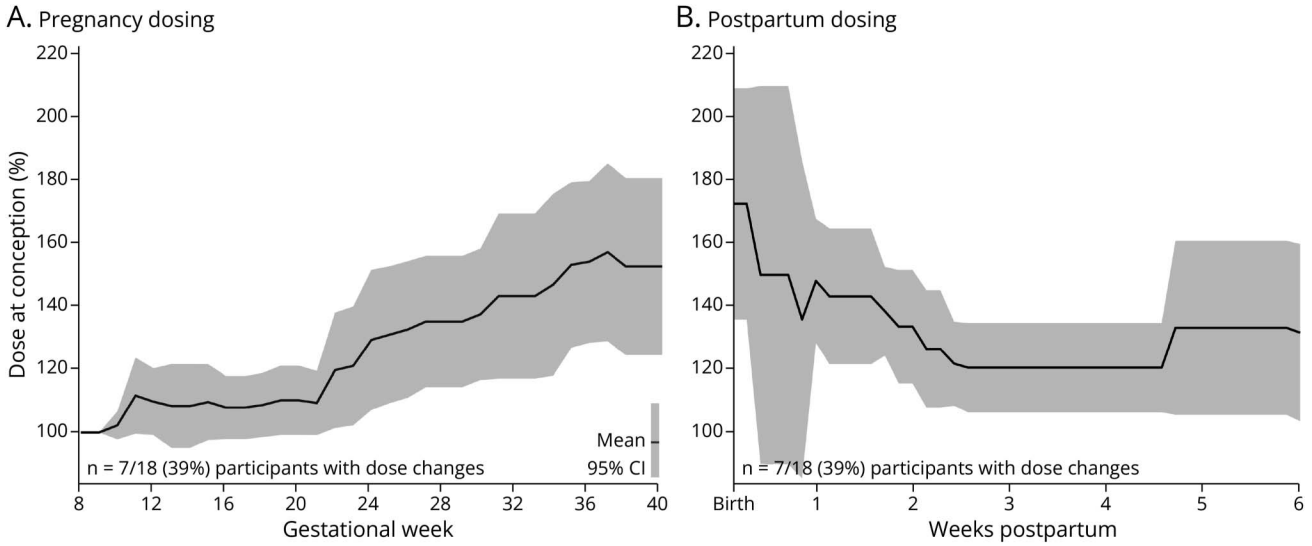
ASMs with ≥10 participants, the timelines are illustrated in eFigures 1 and 2.

ASM Changes From Delivery to 6 Weeks Postpartum

Of the 357 ASM exposures in all participants at the time of delivery, 171 (47.9%) underwent dose changes within 6-week post-delivery. The time to the first dose change occurred median (IQR) 3 (1–8) days post-delivery. Details by each ASM are in Table 2.

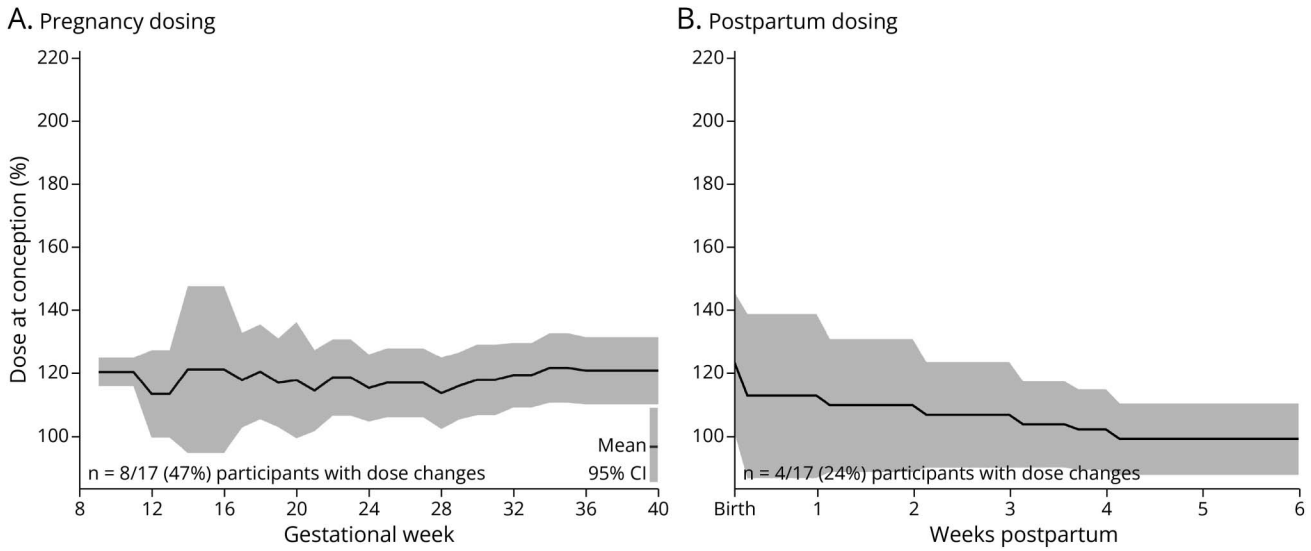
For participants on lamotrigine at delivery, 103/145 (71%) had at least 1 dose change, 46% at least 2, and 24% at least 3 dose changes within 6-week post-delivery. See Figure 2B for

Figure 4 Oxcarbazepine Dosing in Pregnancy and Postpartum



Locally estimated scatterplot smoothing regressions showing the percent of conception dose over time among participants with oxcarbazepine dose changes in pregnancy after enrollment (panel A, 7/18 [39%] participants) and first 6-week postpartum (panel B, 7/18 [39%] participants). The solid line represents the mean, and the gray shading represents the 95% CI. Participants who delivered at or after 34 weeks had their doses at delivery carried forward through gestational week 40 in panel A.

Figure 5 Carbamazepine Dosing in Pregnancy and Postpartum



Locally estimated scatterplot smoothing regressions showing the percent of conception dose over time among participants with carbamazepine dose changes in pregnancy after enrollment (panel A, 8/17 [47%] participants) and first 6-week postpartum (panel B, 4/17 [24%] participants). The solid line represents the mean, and the gray shading represents the 95% CI. Participants who delivered at or after 34 weeks had their doses at delivery carried forward through gestational week 40 in panel A.

an illustration of the timeline. Median (IQR) time to the first dose change was 2 (1–7) days post-delivery, with 4 (4–7) days between the first and second and 4 (3–5) days between the second and third dose changes. Doses were decreased by a median of 100 mg/d for each of the dose changes, with an IQR of 100–200 mg per day for the first change and 50–100 mg per day for the second and third changes. In participants who had a change in dose, the mean (95% CI) dose at 6-week postpartum was 116% (107%–124%) of the conception dose. Compared with early postpartum, there were fewer participants with dose changes between 6 weeks and 9 months postpartum, and the number of and magnitude of ASM dose changes were smaller. The mean dose at 9 months postpartum remained above the baseline conception dose (eFigure 3).

For participants on levetiracetam at delivery 43/123 (35%) changed dose at least once within 6 weeks post-delivery, with 16% and 7.3% with at least 2 and 3 dose changes, respectively (Figure 3B). Median (IQR) time to the first change occurred at 3 (1–8) days post-delivery and time between the first and second dose change was 5.5 (4–7) days, and the second to third change was separated by 3 (3–4) days. Doses were decreased by a median of 500 mg/d for the first 2 changes, with an IQR of 250–625 mg/d for the first change and 343–500 mg/d for the second and a median (IQR) of 375 (250–500) mg/d for the third change. The mean dose at 6-week postpartum was 136% (115%–158%) of conception dose. Compared with early postpartum, the number of and magnitude of ASM dose changes between 6 weeks and 9 months postpartum were smaller. The mean dose at 9 months postpartum remained above the baseline conception-dose (eFigure 4).

Among participants on oxcarbazepine at delivery, 7/18 (39%) changed dose at least once within 6-week post-delivery, and 28% had 2 or more changes (Figure 4B). Median (IQR) time to the first change occurred 7 (6–11) days after delivery. Median time (IQR) between the first to second change was 5 (5–26) days. Dose decreases were median 300 mg/d for the first 2 changes, with an IQR of 300–450 mg/d for the first change and −300 to 300 mg/d for the second. The mean (95% CI) dose at 6 weeks postpartum was 129% (100%–158%) of the conception dose.

For participants on carbamazepine at delivery, 4/17 (24%) changed dose at least once within 6-week of delivery, and 1 participant (5.9%) had 2 or more changes (Figure 5B). Median (IQR) time to the first change occurred 4 (1–12) days post-delivery, with a median (IQR) dose decrease of 150 (100–225) mg/d. The mean (95% CI) dose at 6-week postpartum was 100% (88%–112%) of conception dose.

Of the participants on zonisamide at delivery 4/17 (24%) changed dose at least once within 6 week of delivery, and 11.8% had 2 or more changes. The first dose decrease occurred at a median (IQR) of 6.5 (4–13) days post-delivery, with the second change occurring 6.5 (5.75–7.25) days later. Doses were decreased by a median (IQR) of 100 (87–100) mg/d for the first change and 75 (62–88) mg/d for the second change. The mean (95% CI) dose at 6-week postpartum was 113% (88–137) of the conception dose.

For participants on topiramate at delivery, 3/10 (30%) changed dose at least once within 6 weeks of delivery, with

none having more changes. Median (IQR) time to the first dose decrease occurred at 10 (9–14) days post-delivery, by median (IQR) of 50 (0–75) mg/d. The mean (95% CI) dose at 6-week postpartum was 128% (99%–157%) of the conception dose.

Details about postpartum dose changes for additional ASMs are in Table 2. For zonisamide and topiramate, the other ASMs with ≥10 participants, the timelines are illustrated in eFigures 1 and 2.

Between 6 weeks and 9-month postpartum, there were a small number of changes in ASM doses and the magnitude of dose change also were smaller. Details about later postpartum dose changes (6 weeks to 9-month postpartum) for all ASMs are in eTable 1.

Discussion

Practice guidelines recommend that once patients with epilepsy are pregnant, clinicians should increase the dose of their ASM in response to declining ASM serum levels (concentrations) or worsening seizure control.[25] The specifics are left to the clinician's discretion. Prior literature has not provided details about ASM dosing during pregnancy through postpartum, for example, the magnitude of each dose change, the time point to begin postpartum tapering. These data provide information about the dosing strategies used at MONEAD sites for individual ASMs during and immediately after pregnancy, resulting in favorable seizure outcomes.[33] Following these typical practices can assist clinicians in both maintaining seizure control and reducing the likelihood of medication toxicity during and immediately after pregnancy.[11,30]

Our prior analysis of seizure patterns in MONEAD focused on seizure types that impair consciousness given the high clinical relevance. Approximately one-third of participants had active seizures, reflective of the general adult population with epilepsy. We compared seizure stability and ASM dose changes among PWWE with control NPWWE. Each participant was compared with their individualized baseline seizure frequency. As reported earlier, there was no difference in seizure stability between pregnant and nonpregnant participants,[33] which suggests that these dose changes at least maintained the effectiveness of ASMs throughout pregnancy and the early postpartum period.[33]

Our analysis found that during pregnancy, 87.7% of participants on lamotrigine had at least 1 dose change, and 46.6% had 3 or more changes. For levetiracetam, 56% had at least 1 change, and 16.8% had at least 3 changes. Doses for both ASMs were changed at approximately 4- to 6-week intervals, which may reflect the therapeutic drug monitoring frequency in epilepsy practices with a subspecialty interest in management of epilepsy during pregnancy. Lamotrigine doses were increased by a median of 100 mg/d each time, in contrast to the slower titration of 25–50 mg/d for monotherapy outside of pregnancy. There were no drug rashes or other serious idiosyncratic reactions, which support that these lamotrigine dose incremental changes can be made safely during pregnancy in the setting of increasing clearance.

Doses for many of the ASMs were decreased beginning within a few days after delivery, consistent with the presumed relatively rapid transition to nonpregnant pharmacokinetics after delivery. Studies of postpartum pharmacokinetic changes and time courses for all medications are notably scant.[36] A greater proportion of lamotrigine doses were decreased compared with levetiracetam (71% vs 35%), likely from the risk of symptomatic toxicity of supratherapeutic lamotrigine levels[11,12] compared with the relatively asymptomatic state of supratherapeutic levetiracetam levels. At the end of 6-week postpartum, participants remained on doses that were on average 116% and 136% of their conception dose for lamotrigine and levetiracetam, respectively (Figures 2B and 3B). Other ASMs were similarly maintained at higher doses postpartum. This may have been done to offset the seizure-provoking effects of postpartum sleep deprivation.

We have previously described that a subpopulation of PWWE undergoes minimal changes in lamotrigine clearance during pregnancy[31]; in MONEAD, 9% of PWWE had no significant change in clearance throughout pregnancy.[37] This may partially explain the 39% of participants on lamotrigine without dose change after enrollment. Another discrepancy is in the magnitude of dose changes. In most of the subpopulation (91% of PWWE) in MONEAD, the clearance increased to a maximum of 275% of baseline, nonpregnant clearance.[37] This contrasts with our finding that the dose at delivery was mean 191% of the conception dose for all participants on lamotrigine with dose changes. It is possible that clinicians were reluctant to be aggressive in making maximal dosage adjustments and/or that there was variability in the consistency of therapeutic drug monitoring with frequent, regular ASM concentration measurements. Since this cohort was enrolled and followed in 2012–2016, subsequent studies have dismissed earlier concerns that there are lamotrigine dose-dependent increased risks for major congenital malformations.[38] In addition, our MONEAD analyses did not find elevated risk to neurodevelopment with lamotrigine concentrations in the higher standard therapeutic ranges in the third trimester.[35] Prior publications have identified increased lamotrigine clearance by 5-week gestational age.[8] Our recent population mixed-effects modeling approach to MONEAD data demonstrated that 50% of the maximum clearance increase was reached at 12-week gestational age.[37] It will be important to examine whether prescribing patterns change in light of these newer findings.

Zonisamide, oxcarbazepine, and carbamazepine were the next most commonly prescribed ASMs in our cohort. During pregnancy, oxcarbazepine was increased to mean 153% of

conception dose at delivery. By contrast, the finding of a relatively modest increase in carbamazepine to mean 123% of conception dose at delivery is consistent with prior reports of minimal changes in total carbamazepine clearance and no changes in free carbamazepine clearance.[23,32,39] During pregnancy, there are relatively modest changes in the specific cytochrome P450 3A4 isoenzyme and carbamazepine protein binding decreases, resulting in increased free fraction. The stability of carbamazepine dosing throughout pregnancy can be seen in Figure 4A. Despite the fact that oxcarbazepine is a structural analog of carbamazepine, oxcarbazepine is rapidly converted to its monohydroxy derivative, with a primary elimination pathway through glucuronidation and renal excretion,[40] rather than the cytochrome P450 3A4 enzyme.

Many ASMs are less commonly prescribed in pregnancy and therefore have minimal published data on their dosing in pregnancy and postpartum. We describe how several of these ASMs were managed, within the limitations of small sample sizes for these other ASMs. Almost all ASMs had at least 1 participant with at least 1 dose increase in pregnancy. The primary exceptions were dose decreases in topiramate and valproate, which are ASMs with high teratogenic risk[25,41] and likely drove clinical decision-making. Doses of lorazepam, clonazepam, and pregabalin were not changed in pregnancy or postpartum and may reflect that in our cohort, they were used as part of a polytherapy regimen only. In addition, animal data demonstrating adverse effects of benzodiazepines on the developing brain may have factored into clinical decision-making.[42]

There are limitations to the analysis. Similar to all observational studies, MONEAD is subject to selection bias and unmeasured potential confounders. For example, the MONEAD cohort did not mirror US population demographics by race, ethnicity, or rurality. Potential health equity disparities can also affect the implementation of proactive ASM dose management during pregnancy and early postpartum. These findings need replication in other observational studies because it is unlikely to be addressed in randomized, clinical trials given ethical and practical concerns. It is not possible to know with certainty that dose changes provided benefit, but the dose changes during pregnancy and postpartum were not accompanied by seizure worsening or serious adverse events. The rationale behind ASM dose changes for an individual were not available. Because enrollment occurred up to 20-week gestational age, prospective information on ASM dose changes early in pregnancy and before enrollment is limited. This is an area of active investigation. There were far fewer participants on ASMs other than lamotrigine or levetiracetam; these 2 ASMs were likely chosen by the participant and their clinician in part because of their favorable outcomes for major congenital malformations and neurodevelopment.[25,26,43] Findings from this MONEAD cohort reinforce the favorable neurodevelopmental outcomes for these 2 ASMs; verbal index scores at age 6 years did not differ between children exposed to levetiracetam monotherapy (107.4; 95% CI 104.4–110.4) compared with lamotrigine monotherapy (109.2; 95% CI 106.9–111.5) or compared with children of healthy pregnant women[35] (108.4; 95% CI 106.0–110.9). Clinicians are advised to combine results of this analysis with the information about early clearance changes in managing PWWE.

In conclusion, the results of this analysis describe the frequency and magnitude of ASM changes in pregnancy to maintain seizure stability comparable with that of nonpregnant participants with epilepsy. Early postpartum tapers are also detailed. This unique dataset can assist clinicians in managing ASM dosing in women with epilepsy during pregnancy and early postpartum to achieve favorable maternal and child outcomes.

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Author Contributions

P.B. Pennell: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D. Li: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. W.T. Kerr: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A.M. Pack: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. French: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Gerard: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.K. Birnbaum: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. K.N. McFarlane: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K.J. Meador: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Appendix Coinvestigators

Coinvestigators are listed at Neurology.org/N.

References

1. Nucera B, Brigo F, Trinka E, Kalss G. Treatment and care of women with epilepsy before, during, and after pregnancy: a practical guide. *Ther Adv Neurol Disord*. 2022;15:17562864221101687. doi:10.1177/17562864221101687
2. Christensen J, Vestergaard C, Hammer Bech B. Maternal death in women with epilepsy: smaller scope studies. *Neurology*. 2018;91(18):e1716-e1720. doi:10.1212/wnl.0000000000006426
3. MacDonald SC, Bateman BT, McElrath TF, Hernández-Díaz S. Mortality and morbidity during delivery hospitalization among pregnant women with epilepsy in the United States. *JAMA Neurol*. 2015;72(9):981-988. doi:10.1001/jamaneurol.2015.1017
4. Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. *Epilepsia*. 2014;55(7):e72-e74. doi:10.1111/epi.12621
5. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry*. 2004;75:1575-1583. doi:10.1136/jnnp.2003.029132
6. Ioannou P, Foster DL, Sander JW, et al. The burden of epilepsy and unmet need in people with focal seizures. *Brain Behav*. 2022;12(9):e2589. doi:10.1002/brb3.2589

7. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. *Clin Pharmacokinet*. 2005;44(10):989-1008. doi:10.2165/00003088-200544100-00001
8. Karanam A, Pennell PB, French JA, et al. Lamotrigine clearance increases by 5 weeks gestational age: relationship to estradiol concentrations and gestational age. *Ann Neurol*. 2018;84(4):556-563. doi:10.1002/ana.25321
9. Peck AW. Clinical pharmacology of lamotrigine. *Epilepsia*. 1991;32(suppl 2):S9-S12. doi:10.1111/j.1528-1157.1991.tb05883.x
10. Pennell PB. Antiepileptic drug pharmacokinetics during pregnancy and lactation. *Neurology*. 2003;61(6 suppl 2):S35-S42. doi:10.1212/wnl.61.6_suppl_2.s35
11. Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology*. 2008;70(22 pt 2):2130-2136. doi:10.1212/01.wnl.0000289511.20864.2a
12. Reimers A, Helde G, Bråthen G, Brodtkorb E. Lamotrigine and its N2-glucuronide during pregnancy: the significance of renal clearance and estradiol. *Epilepsy Res*. 2011;94(3):198-205. doi:10.1016/j.eplepsyres.2011.02.002
13. Ohman I, Luef G, Tomson T. Effects of pregnancy and contraception on lamotrigine disposition: new insights through analysis of lamotrigine metabolites. *Seizure*. 2008;17(2):199-202. doi:10.1016/j.seizure.2007.11.017
14. Ohman I, Beck O, Vitols S, Tomson T. Plasma concentrations of lamotrigine and its 2-N-glucuronide metabolite during pregnancy in women with epilepsy. *Epilepsia*. 2008;49(6):1075-1080. doi:10.1111/j.1528-1167.2007.01471.x
15. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia*. 2000;41(6):709-713. doi:10.1111/j.1528-1157.2000.tb00232.x
16. Westin AA, Reimers A, Helde G, Nakken KO, Brodtkorb E. Serum concentration/dose ratio of levetiracetam before, during and after pregnancy. *Seizure*. 2008;17(2):192-198. doi:10.1016/j.seizure.2007.11.027
17. Tomson T, Palm R, Källén K, et al. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia*. 2007;48(6):1111-1116. doi:10.1111/j.1528-1167.2007.01032.x
18. Mazzucchelli I, Onat FY, Ozkara C, et al. Changes in the disposition of oxcarbazepine and its metabolites during pregnancy and the puerperium. *Epilepsia*. 2006;47(3):504-509. doi:10.1111/j.1528-1167.2006.00459.x
19. Wegner I, Edelbroek P, de Haan GJ, Lindhout D, Sander JW. Drug monitoring of lamotrigine and oxcarbazepine combination during pregnancy. *Epilepsia*. 2010;51(12):2500-2502. doi:10.1111/j.1528-1167.2010.02771.x
20. Reimers A, Helde G, Becser Andersen N, et al. Zonisamide serum concentrations during pregnancy. *Epilepsy Res*. 2018;144:25-29. doi:10.1016/j.eplepsyres.2018.05.002
21. Voinescu PE, Park S, Chen LQ, et al. Antiepileptic drug clearances during pregnancy and clinical implications for women with epilepsy. *Neurology*. 2018;91(13):e1228-e1236. doi:10.1212/wnl.0000000000006240
22. Westin AA, Nakken KO, Johannessen SI, Reimers A, Lillestølen KM, Brodtkorb E. Serum concentration/dose ratio of topiramate during pregnancy. *Epilepsia*. 2009;50(3):480-485. doi:10.1111/j.1528-1167.2008.01776.x
23. Johnson EL, Stowe ZN, Ritchie JC, et al. Carbamazepine clearance and seizure stability during pregnancy. *Epilepsy Behav*. 2014;33:49-53. doi:10.1016/j.yebeh.2014.02.011
24. Harden CL, Pennell PB, Koppel BS, et al. Practice parameter update: management issues for women with epilepsy: focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009;73(2):142-149. doi:10.1212/WNL.0b013e3181a6b325
25. Pack AM, Oskoui M, Williams Roberson S, et al. Teratogenesis, perinatal, and neurodevelopmental outcomes after in utero exposure to antiseizure medication: practice guideline from the AAN, AES, and SMFM. *Neurology*. 2024;102(11):e209279. doi:10.1212/WNL.0000000000209279
26. Tomson T, Battino D, Bromley R, et al. Executive summary: management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. *Epilepsia*. 2019;60(12):2343-2345. doi:10.1111/epi.16395
27. Cheung KL, Lafayette RA. Renal physiology of pregnancy. *Adv Chronic Kidney Dis*. 2013;20(3):209-214. doi:10.1053/j.ackd.2013.01.012
28. Kerlan V, Nahoul K, Le Martelot MT, Bercovici JP. Longitudinal study of maternal plasma bioavailable testosterone and androstanediol glucuronide levels during pregnancy. *Clin Endocrinol (Oxf)*. 1994;40(2):263-267. doi:10.1111/j.1365-2265.1994.tb02478.x
29. Voogt JL. Control of hormone release during lactation. *Clin Obstet Gynaecol*. 1978;5(2):435-455. doi:10.1016/s0306-3356(21)00436-2
30. de Haan GJ, Edelbroek P, Segers J, et al. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology*. 2004;63(3):571-573. doi:10.1212/01.wnl.0000133213.10244.fd
31. Polepally AR, Pennell PB, Brundage RC, et al. Model-based lamotrigine clearance changes during pregnancy: clinical implication. *Ann Clin Transl Neurol*. 2014;1(2):99-106. doi:10.1002/acn3.29
32. Pennell PB, Karanam A, Meador KJ, et al. Antiseizure medication concentrations during pregnancy: results from the maternal outcomes and neurodevelopmental effects of antiepileptic drugs (MONEAD) study. *JAMA Neurol*. 2022;79(4):370-379. doi:10.1001/jamaneurol.2021.5487
33. Pennell PB, French JA, May RC, et al. Changes in seizure frequency and antiepileptic therapy during pregnancy. *N Engl J Med*. 2020;383(26):2547-2556. doi:10.1056/NEJMoa2008663
34. Meador KJ, Cohen MJ, Loring DW, et al. Cognitive outcomes at age 3 years in children with fetal exposure to antiseizure medications (MONEAD study) in the USA: a prospective, observational cohort study. *Lancet Neurol*. 2023;22(8):712-722. doi:10.1016/S1474-4422(23)00199-0
35. Meador KJ, Cohen MJ, Loring DW, et al. Neuropsychological outcomes in 6-year-old children of women with epilepsy: a prospective nonrandomized clinical trial. *JAMA Neurol*. 2025;82(1):30-39. doi:10.1001/jamaneurol.2024.3982
36. Van Neste M, Bogaerts A, Nauwelaerts N, et al. Challenges related to acquisition of physiological data for physiologically based pharmacokinetic (PBPK) models in postpartum, lactating women and breastfed infants: c contribution from the ConcePTION project. *Pharmaceutics*. 2023;15(11):2618. doi:10.3390/pharmaceutics15112618
37. Karanam A, Pennell PB, Meador KJ, Long Y, Birnbaum AK. Characterization of lamotrigine disposition changes during and after pregnancy in women with epilepsy. *Pharmacotherapy*. 2025;45(1):33-42. doi:10.1002/phar.4640
38. Battino D, Tomson T, Bonizzoni E, et al. Risk of major congenital malformations and exposure to antiseizure medication monotherapy. *JAMA Neurol*. 2024;81(5):481-489. doi:10.1001/jamaneurol.2024.0258
39. Tomson T, Lindbom U, Ekqvist B, Sundqvist A. Epilepsy and pregnancy: a prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin. *Epilepsia*. 1994;35(1):122-130. doi:10.1111/j.1528-1157.1994.tb02921.x
40. Schmidt D, Elger CE. What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs? *Epilepsy Behav*. 2004;5(5):627-635. doi:10.1016/j.yebeh.2004.07.004
41. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013;12(3):244-252. doi:10.1016/S1474-4422(12)70323-X
42. Kellogg M, Meador KJ. Neurodevelopmental effects of antiepileptic drugs. *Neurochem Res*. 2017;42(7):2065-2070. doi:10.1007/s11064-017-2262-4
43. Bromley R, Adab N, Bluett-Duncan M, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev*. 2023;8(8):CD010224. doi:10.1002/14651858.CD010224.pub3