# Antiepileptic drug clearances during pregnancy and clinical implications for women with epilepsy

P. Emanuela Voinescu, MD, PhD, Suna Park, BS, Li Q. Chen, BA, Zachary N. Stowe, MD, D. Jeffrey Newport, MD, MS, MDiv, James C. Ritchie, PhD, and Page B. Pennell, MD

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#### **Abstract**

#### **Objective**

To characterize the magnitude and time course of pregnancy-related clearance changes for different antiepileptic drugs (AEDs): levetiracetam, oxcarbazepine, topiramate, phenytoin, and valproate. A secondary aim was to determine if a decreased AED serum concentration was associated with increased seizure frequency.

#### **Methods**

Women with epilepsy were enrolled preconception or early in pregnancy and prospectively followed throughout pregnancy and the first postpartum year with daily diaries of AED doses, adherence, and seizures. Study visits with AED concentration measurements occurred every 1–3 months. AED clearances in each trimester were compared to nonpregnant baseline using a mixed linear regression model, with adjustments for age, race, and hours postdose. In women on monotherapy, 2-sample t test was used to compare the ratio to target concentrations (RTC) between women with seizure worsening each trimester and those without.

#### **Results**

AED clearances were calculated for levetiracetam (n = 18 pregnancies), oxcarbazepine (n = 4), topiramate (n = 10), valproate (n = 5), and phenytoin (n = 7). Mean maximal clearances were reached for (1) levetiracetam in first trimester (1.71-fold baseline clearance) (p = 0.0001), (2) oxcarbazepine in second trimester (1.63-fold) (p = 0.0001), and (3) topiramate in second trimester (1.39-fold) (p = 0.025). In 15 women on AED monotherapy, increased seizure frequency in the first, second, and all trimesters was associated with a lower RTC (p < 0.05).

#### **Conclusion**

AED clearance significantly changes by the first trimester for levetiracetam and by the second trimester for oxcarbazepine and topiramate. Lower RTC was associated with seizure worsening. Early therapeutic drug monitoring and dose adjustment may be helpful to avoid increased seizure frequency.

#### Correspondence

Dr. Pennell ppennell@bwh.harvard.edu

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#### Glossary

AED = antiepileptic drug; GA = gestational age; HPD = hours postdose; RTC = ratio to target concentration; TDM = therapeutic drug monitoring.

A challenge of managing epilepsy during pregnancy is the pronounced pharmacokinetic alterations, including increased volume of distribution, elevated renal clearance, and induction of hepatic metabolism. Knowledge about the pattern of gestational age-dependent clearance changes can help guide the timing and range of antiepileptic drug (AED) dose adjustments and contribute to maintaining seizure stability during pregnancy.

In a prior study, we showed that lamotrigine clearance increases significantly throughout pregnancy. 1,2 Using preconception clinical data to determine an individualized target concentration, we calculated the ratio to target concentration (RTC) for each blood draw during pregnancy and identified an RTC threshold of 0.65 as a significant predictor of seizure worsening. In contrast, we showed carbamazepine clearance does not change substantially during pregnancy, and seizure worsening was not associated with lower RTC.3 Therefore, while lamotrigine therapeutic drug monitoring (TDM) is critical, 1,4 carbamazepine TDM may not be necessary for all women during pregnancy. Most of the prior studies on pregnancy-related clearance changes for other AEDs were retrospective, were small, did not account for timing of blood draw relative to last dose intake, and fall short of detecting the importance of TDM for seizure control.

In this prospective, observational study with collection of clinical data and AED serum concentrations throughout pregnancy, we analyzed the range and time course of clearance changes for the remaining AEDs for which we collected samples from at least 4 pregnancies: levetir-acetam, oxcarbazepine, topiramate, phenytoin, and valproic acid. We also compared the RTC values between women with seizure worsening and those without worsening for each trimester.

#### Methods

#### Study population

Women with epilepsy planning to conceive or <16 weeks gestational age (GA) were screened for inclusion in a prospective, observational investigation of pharmacokinetic alterations of AEDs during pregnancy at the Emory Clinic from December 2002 until November 2007. Patients were excluded for age <16 years, uncontrolled thyroid disease, severe anemia, ethanol or illicit drug use, renal or hepatic dysfunction, active suicidal ideation, progressive cerebral disease, known poor AED adherence, or inability to keep a seizure calendar. The current analyses were restricted to women who chose to continue their AEDs during pregnancy and from

whom we obtained at least one baseline, nonpregnant and one pregnant AED clearance value.

### Standard protocol approvals, registrations, and patient consents

The institutional review board of Emory University School of Medicine approved the study. Women were informed of all available treatment options, and written informed consent was obtained.

#### Study design

Study visits occurred every 1-3 months during pregnancy and the first postpartum year. Daily calendars were kept for concomitant medications, any missed AED doses, and for the number and types of seizures. At each study visit, daily seizure medication calendars were reviewed, and maternal blood was collected, with recording of time since the last dose. Separate samples were collected for research and clinical purposes. Additional clinical samples were collected at obstetric office visits. The study protocol did not dictate clinical care decisions. The primary management of seizures and AED dosing was assumed by the project principal investigator (P.B.P.). Results from clinical samples were used for TDM. Recommendations to adjust AED doses were based on the individual's seizure types, epilepsy syndrome, seizure frequency, history of medication-related side effects, and preconception AED concentrations. All blood draws occurred at steady state (at least 5 days after dose adjustment).

#### **Laboratory measurements**

#### Levetiracetam research samples

Maternal blood was collected at research visits between January 2003 and October 2007, and centrifuged at 2,750 rpm at 3°C for 10 minutes. Serum was aliquoted into polypropylene tubes and stored at -80°C until assay date, the earliest in August 2005 and the latest in September 2009. On the assay day, samples were thawed at room temperature, then mixed and incubated at 37°C for 30 minutes and were assayed for total levetiracetam concentration, with utilization of high-resolution, high-performance liquid chromatography with ultraviolet detection method supplied by Chromsystems, GmbH (Munich, Germany). Samples were batched to reduce interassay variability and to allow simultaneous processing of all samples from the same participant, and assays were performed in the research laboratory of Dr. James Ritchie at Emory University by a technician blinded to the participants' identities and doses. Most assays were performed <1 year from collection date, but occasionally up to 2.5 years.

#### **AED clinical samples**

Clinical samples were independently collected in clinical laboratories affiliated with Emory or outside reference laboratories (LabCorp, Arup, National Medical Services, Quest, Southern Regional Medical Center, Newnan Hospital), and processed per each laboratory protocol. Assays were performed <72 hours from collection for clinical decision-making.

The number of samples available for analysis for each participant varied for several reasons: enrollment window was preconception to 16 weeks GA, pregnancy loss, the observational approach with dependence on obtaining complete data from clinical visits in addition to study visits, which could be as infrequent as every trimester, and missing data including weight or hours postdose (HPD).

#### **Data analysis**

Apparent oral clearance was calculated as daily dose (mg/kg)/serum AED concentration (mg/L). Nonpregnant baseline clearance was calculated from the preconception period or, if not available, >4 weeks postpartum. AED clearances were compared between nonpregnant baseline, first trimester (<14 weeks GA), second trimester (14–28 weeks GA), and third trimester (>28 weeks GA to delivery).

### Levetiracetam clearance using research laboratory concentration values

Levetiracetam clearance values were log-transformed to meet the normality assumption. The change in clearance among baseline and trimesters of pregnancy was investigated through mixed linear regression model, as we assumed correlation within the clearance values contributed by the same participant. In the mixed linear model, random intercept was created for each participant ID to account for interindividual variability. We fitted models adjusting for age, race, and HPD, and included square terms as they enhanced the model fit with statistical significance. The influence of HPD and age were accounted for by incorporating quadratic terms of the corresponding variable in the mixed linear regression model.

### AED clearance using clinical laboratory concentration values

Clinical serum concentrations of levetiracetam, the monohydroxy derivative of oxcarbazepine, phenytoin, topiramate, and valproate monotherapy or noninteracting polytherapy were analyzed in a similar way. Clearance values of each were log-transformed and then fit for regression separately. Mixed linear regression was used to account for within-participant correlation with random intercept by each participant ID. For those where the interclass correlation coefficient values between individual participants were close to zero, we also tried fitting simple linear regression with robust variance and got the same coefficients with slightly different p values. Similarly to our LEV analysis, we adjusted for age, HPD, and calculated relative clearance change in each trimester compared to the nonpregnant baseline.

#### Seizure frequency analysis

This was limited to participants on AED monotherapy throughout the pregnancy, with complete seizure history (beginning 1 year prior to pregnancy to the end of pregnancy) and AED concentrations from nonpregnant baseline and at least one trimester. Detailed seizure and epilepsy history was obtained at enrollment and classified per the International League Against Epilepsy classification system at the initiation of the study. 5,6 Retrospective seizure frequency for the year prior to conception was recorded, and seizure occurrence and frequency were obtained prospectively beginning at enrollment. To calculate seizure frequency, the total number of seizures (all types) were divided by number of weeks in respective periods of time. Seizure frequency in each trimester was compared to preconception baseline, and coded as 1 if increased, or as 0 otherwise. RTC was calculated as average serum AED concentration in each trimester divided by average serum AED concentration in nonpregnant baseline. Two-sample t test was used to compare the RTCs between those who experienced seizure worsening during each trimester and those who did not. Significance in different RTC values was determined based on one-tailed p values, as the difference in one direction was considered sufficient for clinical interpretation. We also qualitatively applied the 0.65 threshold, as determined by prior studies, to see if this separated the seizure worsening group in each trimester.

#### **Data availability**

Individual de-identified participant data (including clinical characteristics and antiepileptic medication clearance data) will be shared; the statistical analysis plan will be shared over the next 2 years. The corresponding author will mediate the data transfer upon request.

#### Results

#### **Clinical characteristics of study participants**

Forty women with 44 pregnancies met inclusion criteria for this analysis (table). Another 32 pregnancies in 32 women were not included in these analyses due to study protocol nonadherence or lack of an AED clearance value during nonpregnant baseline or at least once during pregnancy.

All participants on AED monotherapy or polytherapy with a noninteracting AED were included in the clearance analysis. Only participants on AED monotherapy were included in the analysis of seizure frequency and RTC (figure 1).

Among the clinical characteristics, age was a significant covariate for all AEDs, and race was significant for levetiracetam clearance changes.

# Levetiracetam clearance changes during pregnancy

Levetiracetam serum concentrations measured for research and for clinical purposes were analyzed together

**Table** Clinical characteristics of women included in the clearance analysis

Characteristics	LEV	ТРМ	VPA	PHT	охс
Total no. of patients included in the clearance analysis	16	8	5	7	4
Total no. of pregnancies	18	10	5	7	4
Reason for treatment, n (% of total)					
Focal epilepsy	10 (62.5)	4 (50)	1 (20)	5 (71.4)	3 (75)
Generalized epilepsy	5 (31.3)	4 (50)	4 (80)	1 (14.3)	1 (25)
Unclassified epilepsy	1 (6.3)	0	0	1 (14.3)	0
Racial distribution, n (% of total)					
White	10 (62.5)	5 (62.5)	3 (60)	4 (57.1)	3 (75)
Black	5 (31.3)	3 (37.5)	2 (40)	2 (28.6)	0 (0)
Asian	0	0 (0)	0 (0)	1 (14.3)	1 (25)
Native American	1 (6.2)	0 (0)	0 (0)	0 (0)	0 (0)
Mean age, y (range)	27.22 (16–37)	29.26 (17–42)	27.74 (22–34)	29.47 (18–35)	25.52 (23–31)
No. of pregnancies with complete set of samples (baseline and all 3 trimesters)	9	4	3	3	2

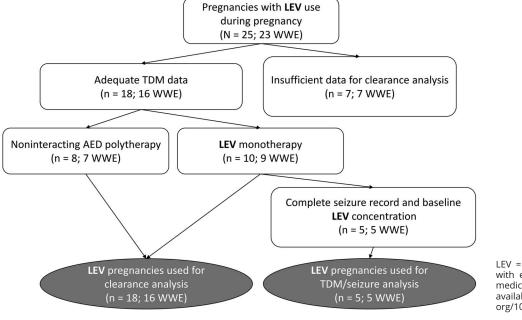
Abbreviations: GA = gestational age; LEV = levetiracetam; OXC = oxcarbazepine; PHT = phenytoin; TPM = topiramate; VPA = valproic acid.

and separately: 106 clinical samples from 16 women with 18 pregnancies were obtained, and 74 research samples were collected from 14 of these women and 16 of these pregnancies. Levetiracetam peak clearance occurs in the first trimester, 1.71-fold baseline clearance (p < 0.0001) (figure 2). The clearance values remain

significantly increased above baseline for the rest of the pregnancy.

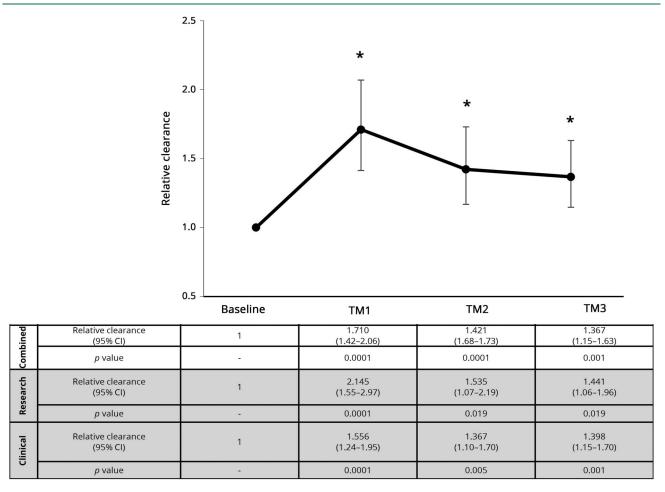
In comparing individuals with more than 5 research observations, we noticed large interindividual variability (e.g., peak of 1.6–4.4-fold baseline clearance).

**Figure 1** Flow diagram for women enrolled in the study and subset used for clearance analysis or therapeutic drug monitoring (TDM)/seizure analysis



LEV = levetiracetam; WWE = women with epilepsy. Flow charts for other medications included in the study data available from Dryad (figure e-1) (doi. org/10.5061/dryad.91f0r82).

Figure 2 Mean relative levetiracetam clearance (95% confidence interval [CI]) by stage of pregnancy



Line chart depicts clearances as reflected by all values available (combined research laboratory and clinical laboratory values). Significant differences, marked by a star on the graph, are seen for each trimester (TM) when compared to the baseline (p < 0.05). Error bars represent 95% CI.

### Clearance changes for oxcarbazepine, topiramate, phenytoin, and valproate

Clinical serum concentrations were used to calculate apparent oral clearance for each AED: 29 concentrations from 4 pregnancies in 4 women on oxcarbazepine, 46 concentrations from 10 pregnancies in 8 women on topiramate, 32 concentrations from 7 pregnancies in 7 women on phenytoin, and 27 concentrations from 5 pregnancies in 5 women on valproate.

Significant clearance changes were noted for oxcarbazepine and topiramate, with a peak in the second trimester to 1.63-fold baseline (p = 0.0001) for oxcarbazepine and 1.39-fold (p = 0.025) for topiramate, and increased values persisted in the third trimester (figure 3). No significant changes in clearance occurred for total or free phenytoin or valproic acid.

# AED concentrations and seizure control during pregnancy

Fifteen women on AED monotherapy with complete seizure history and AED concentrations during nonpregnant baseline and at least one trimester of pregnancy were identified: 4 on levetiracetam, 1 on oxcarbazepine, 2 on phenytoin, 3 on

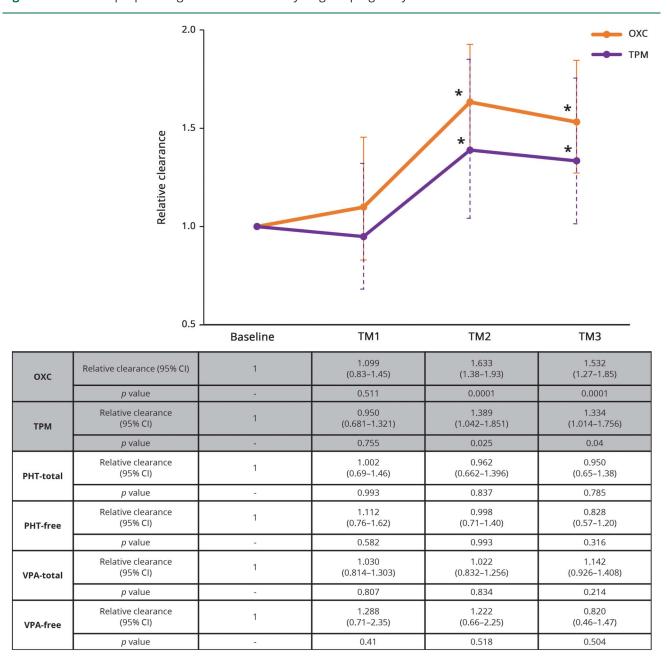
topiramate, and 5 on valproic acid. Twelve of these women had AED concentrations from nonpregnant baseline and all trimesters. Seizure frequency worsening occurred in 6/15 (40%) participants during at least one trimester.

Increased seizure frequency was associated with a lower RTC in the first trimester (p = 0.012), second trimester (p = 0.042), and for the entire pregnancy (p = 0.004), but not for the third trimester (figure 4). In addition, RTC <0.65 was associated with seizure worsening and RTC >0.65 with stable and improved seizure frequency.

#### Discussion

Despite a modest number of participants, these reported findings add to the sparse literature of prospective studies characterizing the magnitude and time course of pregnancy-related clearance changes for several AEDs. We have reported on lamotrigine and carbamazepine previously<sup>1,3</sup> and here we report our findings from analysis of levetiracetam, oxcarbazepine, topiramate, phenytoin, and valproate. While there is some information about clearance changes during pregnancy for these AEDs, prior studies usually

Figure 3 Mean antiepileptic drug relative clearance by stage of pregnancy



Line chart depicts clearances for oxcarbazepine (OXC) (orange line) and topiramate (TPM) (purple line) values. Significant differences, marked by a star on the graph, are seen for the 2nd and 3rd trimester clearance values when compared to the baseline relative values (p < 0.05). CI = confidence interval; PHT = phenytoin; TM = trimester; VPA = valproic acid.

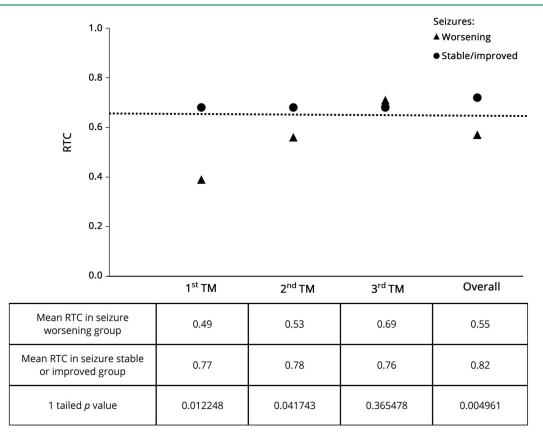
lacked full characterization of the time course of pregnancyrelated clearance changes, and all fell short of identifying a correlation with the clinical course of epilepsy during pregnancy.

Currently, levetiracetam is one of the most frequently used AEDs during pregnancy.<sup>7–11</sup> While other studies previously reported clearance changes during pregnancy, they focused on third trimester values<sup>12</sup> or did not reach statistical significance to draw conclusions on earlier changes.<sup>13</sup> We demonstrate clearance changes early in the first trimester, with an estimated increase to 1.42–2.02-fold baseline clearance. This is important

information for clinicians who manage women on levetiracetam as they may opt to begin TDM as early as possible in pregnancy.

Levetiracetam is mainly excreted unchanged by the kidneys, <sup>14</sup> and the changes in clearance are consistent with the time course of increased glomerular filtration rate during pregnancy. <sup>15</sup> The pathophysiology of the interparticipant variability in clearance fluctuation during pregnancy and of the race influence observed for levetiracetam are difficult to explain with the known pharmacokinetic data. One may speculate that pharmacogenetic differences may be responsible.

Figure 4 Ratio to target concentration (RTC) in seizure worsening vs stable or improved seizure groups



Dashed horizontal line was placed at an RTC of 0.65, previously determined to be a threshold for seizure worsening. TM = trimester.

Our analysis of levetiracetam clearance changes using concentrations from samples processed in a single batch in the same research laboratory led to results similar to those obtained using levetiracetam concentrations from samples processed less homogenously in the clinical laboratories. This is not only an internal control, but it reassures physicians that therapeutic dose monitoring can be reliably done in the clinical outpatient settings and correct conclusions can be drawn about the need for dose adjustments based on the measured serum concentration. However, the most reliable comparison in the clinical setting would be blood draws at approximately the same hour postdose, a significant covariate identified in our study.

The magnitude of levetiracetam clearance increases compared to baseline observed in the research samples and clinical samples differed, but the significant findings were similar. While differences in sample processing protocols between laboratories may have contributed, another probable factor was the interindividual variability we identified. This highlights again the potential benefit of TDM during pregnancy.

Our study also contributes to our understanding of pharmacokinetic changes for oxcarbazepine during pregnancy. Despite evaluation of only 4 pregnancies, we were able to show a significant difference in clearance in the second and third trimesters. Oxcarbazepine is metabolized primarily by glucuronidation, which may explain the similarity to lamotrigine for the clearance changes during pregnancy, although it is unknown if the same isoenzyme, UGT1A4, is involved. Our findings are consistent with those reported by prior studies.<sup>16–18</sup>

We detected a peak topiramate clearance in the second trimester, reinforcing findings reported by prior studies with similar numbers. Although topiramate is eliminated mainly unchanged in the urine, with less than a third metabolized hepatically, we did not detect increased clearance in the first trimester like for levetiracetam.

A caveat of our clearance analysis is that preconception AED concentrations were not available for all participants. We therefore used >4 weeks postpartum values as baseline in our analysis; this has been common practice in prior studies investigating AED pharmacokinetic changes during pregnancy. <sup>12,13,17,20</sup>

Large variation in the HPD can influence the results and accuracy of the conclusions. In this study, blood samples were not drawn at a standard time postdose to reduce the risk of seizures due to holding a dose, and to accommodate participants' scheduling needs including coordinating with

obstetrician appointments. However, we adjusted for the differences in time postdose in our analysis.

Finally, our study did not directly compare seizure outcomes from participants managed with TDM to participants without TDM, and we do not believe that a randomized clinical trial evaluating the efficacy of TDM during pregnancy would be ethical. However, we provide supportive data for the use of TDM to optimize epilepsy management during pregnancy. Patient recruitment for this project was done prior to the 2009 American Academy of Neurology Practice Guidelines, when TDM was not standard practice. Since then, there continues to be some debate whether TDM in pregnancy is necessary or if clinical feature monitoring for signs and symptoms of seizure activity is sufficient. Prior studies evaluated this for lamotrigine<sup>1,21</sup> but the aforementioned studies of other AEDs failed to show a clinical consequence of lowered concentrations during pregnancy. 13,16 A retrospective chart review study reported that for all AEDs, seizures worsened when the AED concentrations fell below 65% of preconception baseline.<sup>22</sup> The same was true in the prospective study of lamotrigine. This prospective study of other AEDs supports the clinical relevance of RTC < 0.65 as an important threshold, with only third trimester values as an outlier. The observed RTC values in the third trimester >0.65 could reflect the physician's efforts to compensate with dose increases for the clearance changes. Additional studies are needed to examine more closely the time course of seizure frequency and AED dose changes at more narrow time intervals, but we were not powered to do such an analysis in our single-center study. In addition, we were not powered to investigate seizure frequency changes by seizure types, and thus we cannot comment on changes in seizure type severity. Additional factors that can affect seizure frequency were not included in this study, e.g., stress, sleep deprivation, and hormone and neuroactive steroid concentrations. A detailed, prospective, multicenter study will be able to better analyze the time course and other variables that could influence seizure control during pregnancy, as well as neonatal and long-term cognitive outcomes of the children. Although this study did not have enough monotherapy participants with complete seizure data and AED concentrations to separately analyze the clinical effect of lower concentrations for individual AEDs, our study demonstrates that women with increased seizure frequency in the first trimester and second trimester have a lower AED RTC, underscoring the importance of close clinical management and potential dosage adjustments beginning early in pregnancy.

This was a small, preliminary study that does not allow for definitive conclusions, yet it suggests clinically relevant findings that require confirmation in studies with a larger number of participants, especially for topiramate and oxcarbazepine. The finding of lower AED RTC at different trimesters suggests that in outpatient clinical practice, possible changes in AED dosing varied by trimester may be clinically important for patient care.

#### **Author contributions**

Dr. Voinescu's contributions include data acquisition, analysis and interpretation, drafting and revising of the manuscript, and preparing the figures. S. Park's contributions include taking the lead on statistical analysis, data interpretation, preparing the figures, and revision of the manuscript. L.Q. Chen's contribution includes acquisition of data and analysis. Dr. Stowe's contributions include study concept and design, obtaining funding, study coordination and supervision, data interpretation, and manuscript revision. Dr. Newport's contributions include study concept and design, obtaining funding, acquisition of data, study coordination and supervision, and manuscript revision. Dr. Ritchie's contributions include study design, obtaining funding, contribution of vital reagents, supervision of serum drug assays, and acquisition of data. Dr. Pennell's contributions include study concept and design, obtaining funding, acquisition of data, study coordination and supervision, data analysis and interpretation, and critical revision of the manuscript for intellectual content.

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