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Lamotrigine in pregnancy:

Clearance, therapeutic drug monitoring, and seizure frequency

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Abstract

Objective—To characterize the magnitude and course of alterations in total and free lamotrigine (LTG) clearance (Cl) during pregnancy and the postpartum period, to assess the impact of therapeutic drug monitoring (TDM) on seizure frequency, to determine the ratio to individual target LTG concentration that is associated with increased seizure risk, and to evaluate maternal postpartum toxicity.

Methods—A cohort of women were enrolled before conception or during pregnancy in this prospective, observational study. Visits occurred every 1 to 3 months with review of seizure and medication diaries, examination, and blood sampling. Total and free LTG CIs were calculated. Individualized target concentrations were used for TDM. The ratio to target concentration (RTC) was compared between patients with and without increased seizures. A receiver operating characteristic curve determined the threshold RTC that best predicts increased seizure frequency.

Results—Analysis of 305 samples in 53 pregnancies demonstrated increased total and free LTG Cl in all trimesters above nonpregnant baseline ($p < 0.001$), with peak increases of 94% and 89% in the third trimester. Free LTG Cl was higher in white compared with black women ($p < 0.05$). Increased seizure frequency ($n = 36$ women with epilepsy) in the second trimester was associated with a lower RTC ($p < 0.001$), and $RTC < 0.65$ was a significant predictor of seizure worsening. An empiric postpartum taper reduced the likelihood of maternal LTG toxicity ($p < 0.05$) ($n = 27$). Newborn outcomes were similar to the general population ($n = 52$).

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Supplemental data at www.neurology.org

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Conclusions—These novel data contribute to a rational treatment plan and dosing paradigm for lamotrigine use during pregnancy, parturition, and the postpartum period.

Lamotrigine (LTG) has emerged as a primary maintenance treatment for women with epilepsy and bipolar disorder during their reproductive years.^{1–3} A major contributor to the use of LTG in this population is the burgeoning pregnancy data that suggest a modest teratogenic risk compared with other antiepileptic drugs (AEDs), with reported rates of major congenital malformations from 1.0% to 5.6%.^{4–9} However, observational studies have indicated that LTG clearance (Cl) markedly increases during pregnancy,^{10–13} with seizures worsening in women with epilepsy.^{10,12} Current treatment guidelines^{14,15} do not address how to dose AEDs after pregnancy is established or through the postpartum period. The vulnerability of the developing fetus must be considered in the context of the necessary maintenance of AEDs for seizure control.

The magnitude of the reported increases in LTG Cl during pregnancy exceeds that described for AEDs that are primarily eliminated via the P450 system.¹⁶ Greater than 90% of LTG is glucuronidated and is controlled primarily by UGT1A4²⁰ and to a lesser extent by UGT1A3.^{17,18} One theory is that the rising sex steroid hormone concentrations enhance expression of UDP-glucuronosyltransferases (UGTs).^{19,20}

An early study (n = 12) reported an increase in LTG oral apparent Cl (>65%) by the second trimester ($p < 0.05$)¹³ but was confounded by coadministration with interacting AEDs in several women. An observational study on LTG monotherapy (n = 14) demonstrated a progressive increase in LTG Cl, with a peak increase of >230% above nonpregnant baseline.¹¹ A retrospective study reported an approximately 150% increase in LTG Cl in the second and third trimesters of pregnancy (n = 11).¹² These studies noted a rapid decrease in LTG Cl during the early postpartum period.^{11–13} Previous investigations have focused on total LTG concentrations. LTG is approximately 55% protein bound. The free fraction of other AEDs increases during pregnancy.¹⁶

Observations of pregnant women with epilepsy taking a variety of AEDs indicate that approximately 17% to 37% of patients will have an increase in their seizures, 7% to 25% will have a decrease in seizures, and 50% to 83% will experience no significant change.^{21,24} Most of these investigations have implicated subtherapeutic AED concentrations as a contributor to increased seizures during pregnancy.^{16,22–24} Generalized tonic-clonic seizures (GTC-Szs) are considered the most dangerous^{25–29} and may even increase the risk for cognitive dysfunction in the offspring.^{30,31}

The alterations in LTG Cl during pregnancy have important clinical relevance. The Australian Pregnancy Registry reported that the rates of failure of control of convulsive seizures were higher for the LTG group compared with the valproate group and the carbamazepine group, with two fetal losses in the LTG group in association with status epilepticus or prolonged seizures.⁸ The physicians in this national population-based study did not tend to use therapeutic drug monitoring (TDM) to make LTG dose adjustments during pregnancy. A study of 12 pregnancies on LTG monotherapy reported that 75% of the pregnancies experienced seizure worsening.¹⁰ After delivery, toxic side effects occurred in three of seven women who had dose adjustments during pregnancy. A retrospective study of LTG monotherapy noted seizure worsening in 45% of the pregnancies (n = 11), occurring in women who had >60% change in level/dose ratio.¹² These retrospective studies did not include a specific paradigm for adjusting LTG dose according to concentration, but did include some adjustments according to their clinical practice.

METHODS

Study population

Women who were pregnant or planning pregnancy who were enrolled in a prospective observational investigation of the pharmacokinetic alterations in AEDs during pregnancy (Emory Women's Epilepsy and Mental Health Programs) from December 2002 until March 2006 were screened for inclusion in the present study. 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. Only women who chose to continue LTG during pregnancy were included in this cohort analysis. Subjects were excluded for uncontrolled thyroid disease, severe anemia, ethanol or recreational drug abuse, renal or hepatic dysfunction, poor compliance, age < 17 years, active suicidal ideations, progressive cerebral disease, inability to keep a seizure calendar personally or by a caregiver, and coadministration of medications known to influence the metabolism of LTG. If a patient had more than one pregnancy during the study, only the most recent completed pregnancy was considered in all analyses.

Study design

Women were enrolled at different gestational ages (GAs) including preconception, and follow-up visits occurred every 1 to 3 months during pregnancy and the first postpartum year. Daily calendars were kept for concomitant medication exposures, for any missed doses of LTG, and for recording number and types of seizures for patients with epilepsy. At each visit, a neurologic examination was performed, the daily seizure-medication calendars were reviewed, and intervening illnesses and maternal or newborn complications were recorded. Maternal blood was collected at each study visit and occasionally at obstetric offices, with recording of number of hours since the last dose of LTG. Medical records were obtained for review from the treating obstetrician, the delivery hospital, and the treating pediatrician.

Laboratory measurements

At each collection, maternal blood was centrifuged at 2,750 rpm at 3°C for 10 minutes, and transferred in 600- μ L aliquots to polypropylene tubes. The samples were stored at -80°C until assay. Maternal sera samples were assayed for total and free LTG concentrations using the high-resolution high-performance liquid chromatography with ultraviolet detection method supplied by Chromsystems, GmbH (Munich, Germany).³² The system has a limit of detection of 0.25 μ g/mL and is linear to 20 μ g/mL for LTG. The intra-assay coefficients of variation (CVs) were 3.0%, 2.0%, and 3.2% for samples with means of 1.50, 9.67, and 14.12 μ g/mL for LTG during this study. The interassay CVs were 12.3%, 7.5%, and 12.5% for samples with means of 1.50, 9.67, and 14.12 μ g/mL for LTG. Free LTG was separated from bound using Centifree YM-30 cartridges (Millipore Corp, Bedford, MA). The ultrafiltrate was assayed in the system described above without modification. The batched assays were performed masked to the patients' identities and LTG doses.

Data analysis

Statistical analysis was performed by Limin Peng, PhD, Assistant Professor in the Department of Biostatistics, Rollins School of Public Health, Emory University.

LTG clearance—Given that oral bioavailability could not be directly calculated from this population pharmacokinetic approach, we calculated LTG apparent oral Cl. LTG apparent oral Cls were calculated for both total LTG and for free (unbound) LTG: $\text{LTG Cl} = \text{daily dose (mg/kg)}/\text{serum LTG concentration (mg/L)}$.

Total and free LTG CIs were compared between different stages of pregnancy: baseline (preconception), first trimester (<14 weeks GA), second trimester (14 to 28 weeks GA), third trimester (29 to 42 weeks GA), and postpartum. For those patients who did not enroll before conception, baseline (nonpregnant) LTG CI was calculated from samples obtained at greater than 6 weeks postpartum and if the patient was not breastfeeding.

To investigate the change of LTG CI among baseline and pregnancy trimesters, we fit a linear mixed model. We examined the change in LTG CI throughout the course of pregnancy by testing the difference between the effects of the different trimesters. We also investigated the effects of race and age on LTG CI. In the model, we assumed constant within-patient correlation. We accounted for the influence of hour post dose of maternal blood collection by incorporating linear and quadratic terms of the corresponding variable. Logarithm transformation was taken to meet the assumption of normality.

Analysis of LTG therapeutic drug monitoring and seizure frequency—In a subgroup of women with epilepsy on LTG monotherapy who had adequate baseline information about seizure frequency and preconception target LTG concentrations, we examined the association between LTG concentrations and seizure frequency. Although this observational, prospective study did not dictate a particular treatment paradigm, if a patient was enrolled in the study with epilepsy, primary management of her seizures and LTG dosing was assumed by one of two investigators (P.B.P. or A.K.). Results of the LTG serum concentrations were actively used for TDM. Recommendations to adjust LTG dosages were made according to the patient's seizure types, epilepsy syndrome, seizure frequency, history of medication-related side effects, and what was considered that individual's target concentration based on all of these factors. GA of pregnancy and hours post dose that the blood was collected were also considered.

For each month of study participation, we coded the relative frequency of all types of seizures as 1 if the frequency was greater than the baseline monthly frequency, and 0 otherwise. If the patient had a history of GTCSzs, the relative frequency of GTCSzs was analyzed in the same manner. For each month, we calculated the ratio to target concentration (RTC), which denotes the ratio of total LTG concentration/ target LTG concentration from nonpregnant baseline. The *t* test was used to compare the RTC values of patients who had an increased seizure frequency (of all types) with the RTC values of those who did not, for each trimester.

Determination of RTC threshold for predicting increased seizure frequency—We calculated the threshold of RTC that best predicted increased seizure frequency. Using a receiver operating characteristic curve (ROC), we determined a reasonable threshold value of RTC which would diagnose a high susceptibility to increased seizure frequency.³³ We restricted our attention to the second trimester, in which we found a strong association between LTG TDM and seizure frequency. Reduction of the RTC below some threshold was viewed as a positive test for diagnosing increased seizure susceptibility. The ROC curve was obtained by plotting true-positive rate vs false-positive rate.

Association of LTG dose and maternal postpartum toxicity—Patients with epilepsy who had adequate follow-up through the early postpartum stage were assessed for symptoms of LTG toxicity. Toxicity symptoms included dizziness, imbalance, and blurred or double vision. During the latter half of study, the treating physicians (P.B.P., A.K.) began prescribing empiric postpartum taper schedules to decrease the dose by steady increments at postpartum days 3, 7, and 10, with return to preconception dose or preconception dose plus 50 mg to help counteract the effects of sleep deprivation.

Association of LTG exposure and seizures and fetal outcome—Logistic regression models were fitted to binary outcomes (yes/no) for small for gestational age (SGA), low birth weight (LBW), admission to special care nursery or neonatal intensive care unit (NICU), Apgar score at 1 minute ≤ 7 , and Apgar score at 5 minutes ≤ 7 . The predictors were chosen as the LTG exposure in the first trimester, second trimester, and third trimester, the total LTG exposure during pregnancy, the occurrence of any seizures, and the occurrence of GTCSzs during pregnancy. The LTG exposure was calculated as the area under the curve (AUC) for LTG dose prescribed.

RESULTS

Fifty-three pregnancies in 53 women met criteria for inclusion in this study (figure 1 and table 1). All women, independent of diagnosis, were included in the analysis of alterations in LTG CI during pregnancy and outcome. Only the patients with epilepsy on LTG monotherapy were included in the analysis of seizure frequency and TDM.

LTG clearance across pregnancy and the postpartum period

Total and free LTG CIs were calculated from 305 samples in the 53 women throughout the course of pregnancy and postpartum period (figures 1 and 2, and figures e-1 and e-2 and table e-1 on the *Neurology*[®] Web site at www.neurology.org). Six of the 53 women had a preconception baseline sample, and postpartum samples (>6 weeks) were used as nonpregnant baseline in another 19 nonlactating women. Application of the linear mixed model revealed that total and free LTG CI rates in each of the pregnancy trimesters were all different from baseline CI rates ($p < 0.001$; figure 2). Both total and free LTG CIs were different in the second and third trimesters from total and free LTG CIs in the first trimester ($p < 0.03$). A difference in free LTG CI was observed between white and black patients ($p = 0.031$), with the white patients exhibiting a higher CI. This trend was not significant for total LTG CI. An increase in hour post dose was associated with an increase in both total LTG CI and free LTG CI ($p < 0.001$). However, the influence of hour post dose was accounted for by incorporating linear and quadratic terms of the corresponding variable in the model. Age had no significant effect on total or free LTG CI.

Analysis of LTG therapeutic drug monitoring and seizure frequency

Thirty-six patients of 39 with epilepsy had adequate baseline information about seizure frequency and preconception target LTG concentrations (table 2). Eighty-three RTC calculations were included. The percentage of patients who had an increase in seizures of all types are plotted in figure 3, along with the free LTG CI by month GA and postpartum. Increased seizure frequency occurred in the highest percentage of patients in the seventh month of gestation (23.5%). For the entire pregnancy, 39% of women had an increase in any type of seizure above preconception baseline, 33% had a decrease in seizures, and 28% had no change.

Comparisons using *t* tests were performed to compare the RTC values of patients who had an increased seizure frequency (of all types) in the second trimester with the RTC values of those who did not. In the second trimester, increased seizure frequency was associated with a lower RTC in the second trimester ($p < 0.001$). Using two other thresholds of increased seizure frequency (1.5-fold increase or 2-fold increase in seizures), the same findings occurred ($p < 0.001$). The associations were not significant in the first trimester or in the third trimester.

Thirty-one patients had a history of GTCSzs. GTCSz frequency doubled or more in 10% of the pregnancies during the sixth month (table 2), but the impact of RTC on GTCSz

frequency was not significant. This may be due to the low number of patients with a history of GTCSzs in the past year (n= 9).

Determination of RTC threshold for predicting increased seizure frequency

Using the ROC curve for predicting increased seizure frequency, a high true-positive rate of 83.3% at a low cost of a false-positive rate of 4.2% was achieved at RTC = 0.65. Increasing the threshold to RTC = 0.78 increased the true-positive rate to 100% but increased the false-positive rate from 4.2% to 25.0%.

Association of LTG dose and maternal postpartum toxicity

Among 27 patients with a clear record on adherence to the empiric taper schedule, 4 of 6 patients who did not follow the taper schedule experienced postpartum toxicity, compared with only 3 of 21 patients who adhered to the taper schedule. A χ^2 test with continuity correction revealed that nonadherence to the standard taper schedule was associated with a higher risk of experiencing postpartum toxicity ($p = 0.040$).

Association of LTG exposure and seizures and fetal outcome

The data included 52 patients whose LTG dosage records were tracked since the first trimester of pregnancy. No significant associations were found between the newborn outcomes SGA, LBW, NICU admissions or Apgar scores < 7, and the AUC of LTG prescribed during each trimester or the entire pregnancy, or the occurrence of any seizures or GTCSzs. Neonatal birth weights were comparable to national statistics.³⁴ No stillbirths occurred; one congenital malformation, renal hydronephrosis, was detected, which was nearly resolved by 4 months of age. One newborn was diagnosed with a heart murmur, which resolved by the first well-baby visit. Two deliveries occurred prematurely, at 32 and 36.3 weeks GA.

DISCUSSION

This study demonstrates significant increases in total LTG CI and free LTG CI between nonpregnant baseline and all trimesters of pregnancy, and between the first trimester and the latter trimesters of pregnancy. The mean total LTG CI increased by 94% and the free LTG CI increased by 89% in the third trimester above the nonpregnant baseline. The magnitude of alteration in total LTG CI is in the middle of the range of previous reports with smaller patient sample sets.¹⁰⁻¹³ Substantial interindividual variability in the degree of enhanced CI has been noted previously¹¹⁻¹³ and may contribute to the differences reported. Interestingly, this larger study noted a racial difference, with white patients showing higher LTG CI rates. The previous studies may have had a different racial mix. Pharmacogenetic variability of UGT1A4 and possibly UGT1A3 polymorphisms³⁵ likely contributes to baseline LTG CI rates and the degree of enhanced CI during pregnancy.

Our analysis of the effectiveness of TDM with total LTG concentrations during pregnancy demonstrates improved seizure control compared with previous reports of LTG use during pregnancy.^{8,10,12} Although 39% of women had an increase in any type of seizure above preconception baseline during pregnancy, 33% actually had a decrease in seizures, and 28% experienced no change. These rates are more consistent with what has been reported for all women with epilepsy on a variety of AED regimens.

The finding of an association between RTC was most robust in the second trimester (14 to 28 weeks), when the largest percentage of patients experienced increased seizures. Our detailed statistical analysis indicates that an RTC < 0.65 in the second trimester is a reliable predictor of seizure worsening. Thus, this data-driven threshold index of a 65% ratio to

target LTG concentration should be used for introducing a dosage adjustment for women with epilepsy on LTG during pregnancy. Given that free LTG concentration measurements are not readily available in the clinical setting, measurement of total LTG is adequate for predicting seizure worsening.

Although the RTC does require a simple calculation with consideration of a patient's target concentration, it is necessary to account for individual differences. The target concentration for each patient is the ideal concentration at which seizures are well controlled without adverse effects. This varies between patients according to epilepsy syndrome, seizure types, and disease severity. Ideally, this target concentration should be established for each woman before pregnancy, but if no preconception baseline is obtained, the practitioner can estimate her target concentration based on these factors.

The return to nonpregnant baseline of total and free LTG CI rates occurred very quickly and within the first month postpartum (figure 3). More than one quarter of the epilepsy patients did experience postpartum toxicity, which was more likely to occur if the postpartum taper was not performed. The risk of postpartum toxicity must be balanced against the necessary adjustments in LTG dose to maintain seizure control during pregnancy, and an empiric postpartum taper is an effective approach to reduce toxicity.

The lack of an association between the amount of LTG dose administered and newborn outcomes suggests that TDM with adjustment of LTG doses during pregnancy may not adversely affect newborn health. However, this study was not powered to detect an increased risk of congenital malformations and the findings need to be considered in light of a report from the UK Epilepsy and Pregnancy Register of a dose-related risk for LTG in the first trimester and major congenital malformations.⁷ However, a logistic regression analysis of the International Lamotrigine Pregnancy Registry data showed no difference in the risk for major malformations as a function of dose.⁴ Additionally, this study did not assess long-term neurocognitive outcomes. Whether the clinical utility of TDM of LTG during pregnancy can be extended to bipolar patients is unclear and under investigation.

This study provides characterization and quantification of the changes in total and free LTG CI across pregnancy and incorporates this novel data into a TDM approach that can provide the foundation for treatment guidelines to prevent increased seizure frequency and improve maternal and fetal health. Future studies should include formal population pharmacokinetic modeling of the alterations in LTG throughout the course of pregnancy and postpartum stages, individual genotyping of UGT1A4/UGT1A3 polymorphisms, exploration of racial differences, and larger sample sets to more thoroughly assess maternal and fetal outcomes, including long-term neurodevelopment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY

AED	antiepileptic drug
AUC	area under the curve

CI	clearance
CV	coefficient of variation
GA	gestational age
GTCSz	generalized tonic– clonic seizure
LBW	low birth weight
LTG	lamotrigine
NICU	neonatal intensive care unit
PP	postpartum month
RTC	ratio to target concentration
SGA	small for gestational age
TDM	therapeutic drug monitoring
UGT	UDP-glucuronosyltransferase

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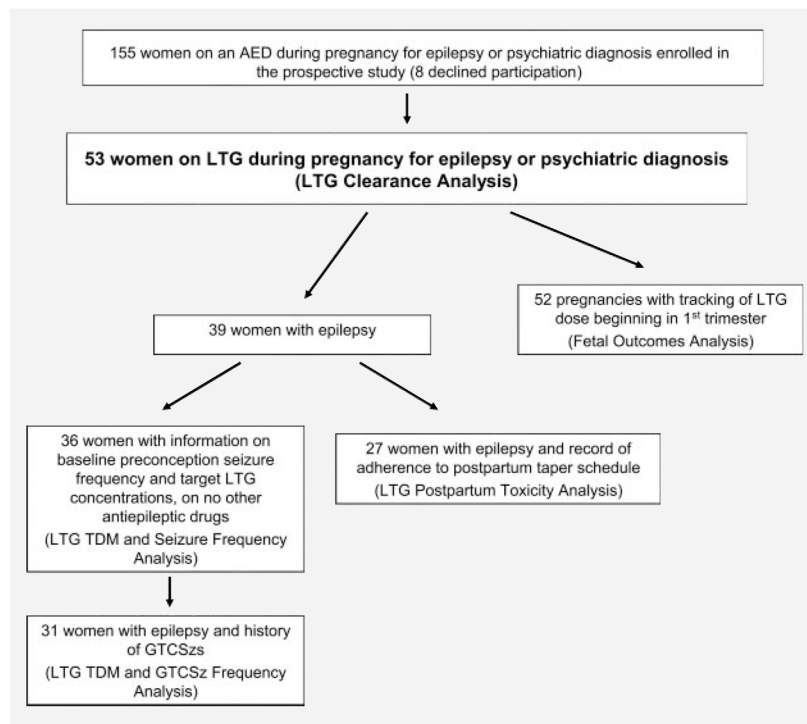


Figure 1. Flow diagram of women enrolled in the study and information used for data analysis. AED = antiepileptic drug; GTCSz = generalized tonic-clonic seizure; LTG = lamotrigine; TDM = therapeutic drug monitoring.

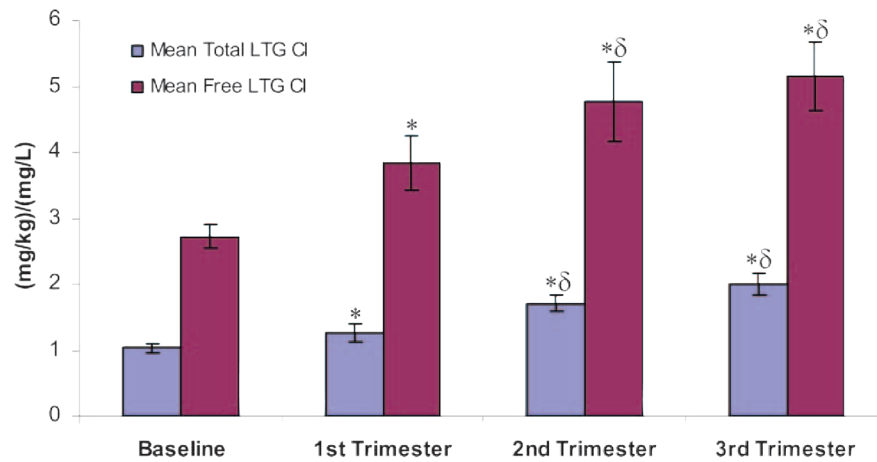


Figure 2.

Total and free lamotrigine clearance during pregnancy

Mean (\pm SE) total lamotrigine clearance (LTG daily dose [mg/kg]/LTG concentration [mg/L]) and mean (\pm SE) free lamotrigine clearance (LTG daily dose [mg/kg]/unbound LTG concentration [mg/L]) during nonpregnant baseline and each trimester of pregnancy. * $p < 0.001$ compared with nonpregnant baseline. $\delta p < 0.03$ compared with first trimester. CI = clearance.

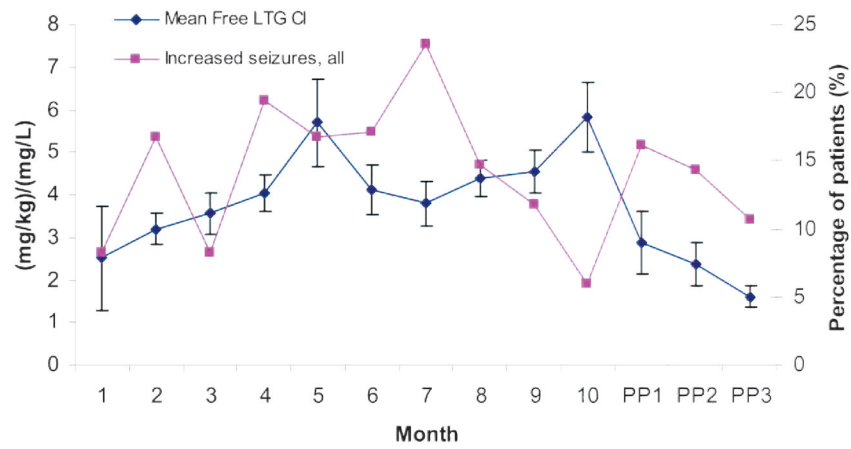


Figure 3.
Lamotrigine clearance and seizures during pregnancy and postpartum
Mean (\pm SE) free lamotrigine clearance (LTG daily dose [mg/kg]/LTG concentration [mg/L]) and percentage of patients who had an increase in seizure frequency compared with preconception baseline, by month gestational age and month postpartum. Cl = clearance.

Table 1

Study population characteristics

Total no. of patients	53
Primary diagnosis	n (% of total)
Psychiatric diagnosis	14 (26.4)
Epilepsy	39 (73.6)
Juvenile myoclonic epilepsy	10 (18.9)
Primary generalized epilepsy, unspecified	2 (3.8)
Localization-related epilepsy	22 (41.5)
Epilepsy, unclear whether focal or generalized	5 (9.4)
Racial distribution, n (% of total)	
White	38 (71.7)
Black (African-American)	9 (17.0)
Asian	4 (7.5)
White-Hispanic	2 (3.8)
Marital status, n (% of total)	
Married	40 (75.5)
Single	13 (24.5)
Tobacco use, n (% of total)	3 (5.7)
Folic acid/vitamin use at time of enrollment, n (% of total)	53 (100)
Mean age (range), y	31.0 (17–42)
Mean education (range), y	15.4 (10–22)
Mean gravida (range)	2.2 (1–10)
Mean gestational age at delivery (range), wk	38.9 (32.1–41.3)

Table 2

Percentages of patients who had an increase or a doubling or more in increased seizure frequency compared with preconception baseline, for all seizure types (n = 36) and for generalized tonic-clonic seizures (n = 31) by month gestational age and month postpartum

Month	1	2	3	4	5	6	7	8	9	10	PP1	PP2	PP3
Increased seizures, all types	8.3	16.7	8.3	19.4	16.7	17.1	23.5	14.7	11.8	5.9	16.1	14.3	10.7
Doubled seizures, all types	8.3	13.9	5.6	16.7	13.9	14.3	17.6	8.8	11.8	2.9	6.5	7.1	3.6
Increased GTCSzs	6.7	0	0	3.3	6.7	10.3	3.6	0	7.1	0	3.8	0	0
Doubled GTCSzs	6.7	0	0	3.3	6.7	10.3	3.6	0	7.1	0	3.8	0	0

PP = postpartum month; GTCSz = generalized tonic-clonic seizure.