Published in final edited form as:

Epilepsy Behav. 2014 April ; 33: 49–53. doi:10.1016/j.yebeh.2014.02.011.

Carbamazepine Clearance and Seizure Stability during Pregnancy

Emily L. Johnson^a, Zachary N. Stowe^c, James C. Ritchie^{e,f}, D. Jeffrey Newport^d, Melanee L. Newman^g, Bettina Knight^c, and Page B. Pennell^{a,b}

^aDepartment of Neurology, Harvard Medical School, Boston, Massachusetts, USA

^bDivision of Women's Health at Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

^cDepartment of Psychiatry, Pediatrics, and Obstetrics & Gynecology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

^dDepartments of Psychiatry and Behavioral Health and Obstetrics & Gynecology, The Ohio State University College of Medicine, Columbus, Ohio, USA

^eDepartment of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia, USA

^fDepartment of Pathology, Emory University School of Medicine, Atlanta, Georgia, USA

^gDepartment of Neurology, Emory University School of Medicine, Atlanta, Georgia, USA

Abstract

The aims of this study were to characterize the alterations in total and free carbamazepine (CBZ) and total and free carbamazepine-epoxide (CBZ-EPO) clearances during pregnancy; to calculate the change in free fractions of CBZ and CBZ-EPO during pregnancy; and to determine whether seizure worsening is associated with a low ratio to non-pregnant baseline concentration of total or free CBZ or CBZ-EPO. Women on CBZ were enrolled before conception or during pregnancy in this prospective, observational study. Concomitant medications and seizure frequency were recorded. Serum total and free CBZ and CBZ-EPO were collected at each visit. Changes in clearance of all four compounds and free fractions of CBZ and CBZ-EPO were compared to non-pregnant baseline. During pregnancy, the ratios to baseline concentrations of total and free CBZ

© 2014 Elsevier Inc. All rights reserved.

Corresponding author: Page B. Pennell, MD, Associate Professor of Neurology, Harvard Medical School, Director of Research, Division of Epilepsy, Division of Women's Health, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, 1-617-732-7557, ppennell@partners.org.

Disclosures: Dr. Ritchie has consulted for Beckman Coulter, Roche, Seimans, and T2Biosciences, none of which are relevant to the current study. During his career, Dr. Newport has received research support from Eli Lilly, Glaxo SmithKline (GSK), Janssen, the National Alliance for Research on Schizophrenia and Depression (NARSAD), the National Institutes of Health (NIH), and Wyeth. He has served on speakers' bureaus and/or received honoraria from Astra-Zeneca, Eli Lilly, GSK, Pfizer and Wyeth. He has served on advisory boards for GSK. The remaining authors have no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and CBZ-EPO were compared for months with and without increased seizure frequency. Total and free CBZ and CBZ-EPO clearances were calculated in 15 pregnancies in 12 women. Clearances did not change for any of these compounds during pregnancy. The free fraction of CBZ increased from 0.23 at baseline to a maximum of 0.32 in the third trimester ($p=0.008$). In the six women on CBZ monotherapy with adequate seizure diaries and blood sampling, seizure worsening did not correspond to a ratio to baseline concentration of less than 0.65 for total or free CBZ or CBZ-EPO. In conclusion, total and free CBZ and CBZ-epoxide clearances did not change substantially during pregnancy, and seizure frequency worsening was not associated with decreased concentrations of total or free CBZ; therefore, therapeutic drug monitoring may not be necessary for all women on CBZ during pregnancy. Further studies with larger sample sizes are needed before definitive recommendations can be made. CBZ monotherapy may be a relatively safe and cost effective treatment option for women with focal epilepsy syndromes during pregnancy.

Keywords

epilepsy; pregnancy; carbamazepine; seizure; clearance; free carbamazepine

1. Introduction

Approximately three to five births per thousand are to women with epilepsy [1]. Carbamazepine (CBZ) is a viable and important option for women with focal epilepsy during their childbearing years due to its low cost, wide availability, relative safety for fetal outcomes, and effectiveness during pregnancy.

CBZ is one of the most widely available anti-epileptic drugs internationally, available in 92 of the 114 countries on which data is available [3], and is relatively inexpensive compared to many of the newer AEDs. Recent reports of the rate of major congenital malformations in children born to women on CBZ include a rate of 3.0% (95% confidence intervals (CI) 2.1–4.2%) in the North American AED pregnancy registry study for all doses [4], and a rate of 3.4% (95% CI 1.11–7.71%) for low-dose CBZ in the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) study [5]. However, EURAP did report higher rates of 5.3% (4.07–6.89%) and 8.7% (5.24–13.39%) in the intermediate- and high-dose CBZ groups [5]. The risk of poor neurodevelopmental outcomes is low with *in utero* CBZ exposure; at age 6 years old, the adjusted mean intelligence quotient (IQ) was 105 (95% CI 102–108) for the CBZ group compared to the population normative IQ score of 100 in the neurodevelopmental effects of antiepileptic drugs (NEAD) study [6].

CBZ is 70–80% protein-bound in the non-pregnant state, and the major route of metabolism is the hepatic cytochrome P450 3A4 isoenzyme. The increase in plasma volume during pregnancy, combined with a relative decrease in the concentration of the major binding proteins albumin and alpha-1-acid glycoprotein during pregnancy, have the potential to affect total and free (unbound) CBZ levels in different patterns [7,8]. CBZ is metabolized to carbamazepine 10,11-epoxide (CBZ-EPO), which is considered not only an active anticonvulsant but also has potential for structural and neurodevelopmental teratogenic effects [8].

While some antiepileptic drugs (AEDs) such as lamotrigine (LTG) are now known to have greatly increased clearance and subsequent decrease in serum levels during pregnancy requiring dose adjustment to prevent seizure worsening [2], data regarding change in clearance of CBZ not as well characterized. Reports of total CBZ levels vary from no change to a 42% decrease; changes in free CBZ from no change to 28% decrease; and clearance of CBZ has produced mixed results ranging from -11% to +27% [9,10,11,12,13]. The largest study of patients on CBZ monotherapy (n=35) reported a decrease in total CBZ concentration (from 23.9uM to 21.0uM), with no change in free CBZ levels, from baseline to the third trimester [12]. This study of 35 women on CBZ did not examine total or free CBZ-EPO [12].

Reports of seizure control during pregnancy agree that most (54–80%) women with epilepsy have unchanged seizure frequency, although seizure frequency increases in 14–32% of pregnant women [14]. Potential changes in the clearance of AEDs during pregnancy prompted studies evaluating the possible association between seizure worsening and changes in maternal AED concentration compared to the preconception baseline. A ratio to non-pregnant baseline concentration of 0.65 has been correlated with increased seizure frequency during the second trimester for LTG monotherapy and for all AEDs combined [2, 15]. No correlation between lower CBZ levels during pregnancy and worsened seizure control has been identified.

CBZ is highly effective during pregnancy. Investigators from EURAP reported that for the women on CBZ monotherapy, 67.3% remained seizure free compared to 58.2% of women on LTG monotherapy, and worsening seizure control in the second and the third trimesters compared to the first trimester was more common in pregnancies exposed to LTG (19.9%) than in those exposed to CBZ (14.6%) [16]. Additionally, women on CBZ had the dose increased and/or another AED added in only 16.7% of pregnancies, compared to a dose increase and/or other AED added in 35.2% of pregnancies on the other AEDs studied (VPA, PB, and LTG) [16]. However, given the magnitude and design of this pregnancy registry, no information is available on serum drug levels or the reasons for making treatment changes. Findings from this current study can help elucidate the potential reasons for the low percentage of women on CBZ requiring a dose increase or addition of another AED, as well as the low percentage of women with seizure worsening.

2. Methods

2.1. Study population

Women with epilepsy or a movement disorder who were planning to conceive or pregnant (<16 weeks gestation) were enrolled in a prospective observational investigation of the pharmacokinetic alterations in AEDs during pregnancy at the Emory Clinic. The Institutional Review Board of Emory University School of Medicine approved the study. Written informed consent was obtained. The current analyses were restricted to women who chose to continue CBZ during pregnancy. Subjects were excluded for uncontrolled thyroid disease, severe anemia, ethanol or illicit drug use, renal or hepatic dysfunction, known poor AED compliance, age <17 years, active suicidal ideation, progressive cerebral disease, or inability to keep a seizure calendar. Only subjects with three or more blood collections in at

least two or more time intervals (non pregnant baseline, first trimester (<14 weeks gestation age [GA]), second trimester [14–28 weeks GA], and third trimester [>28weeks GA]) were included.

2.2. Study design

Women were enrolled at various 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 exposure, any missed doses, and the number and type of seizures. At each visit, a neurological examination was performed, the daily seizure-medication calendars were reviewed, and intervening illnesses or obstetrical 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 AED. Obstetrical and delivery records were obtained and reviewed.

The study protocol did not dictate clinical care decisions. The primary management of seizures and CBZ dosing was assumed by the project principal investigator and epileptologist (P.B.P.). Results from clinically-obtained CBZ serum concentrations were actively used for therapeutic drug monitoring (TDM). Recommendations to adjust AED 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 when the sample was collected were also considered.

2.3. Laboratory measurements

Maternal blood collected via standard venipuncture centrifuged at 2,750rpm at 3°C for 10 minutes, and the serum was stored in 300-μL aliquots in polypropylene tubes and stored at –80°C until assay. Maternal sera samples were assayed for total and free CBZ, and total and free CBZ-EPO concentrations using the high-resolution high-performance liquid chromatography with ultraviolet detection method supplied by Chromsystems, GmbH (Munich, Germany). The batched assays were performed by technologists masked to the patients' identities and AED doses. On the day of measurement samples were thawed at room temperature and then mixed and incubated at 37°C for 30 minutes. For free drug determination of each compound 500 μL of sample was placed in an Amicon Ultra microfilter (3,000 molecular weight cutoff, Millipore Inc., Billerica, MA) and centrifuged at 3500xG for 30 minutes at 37°C. 100 μL of the ultrafiltrate was then extracted as per the kit procedure. For the unbound samples 40 μL was injected onto the HPLC rather than the usual 20μL. The assay was performed using an HPLC column supplied with the kit on an Agilent 1100 HPLC system. The limit of detection of all compounds (bound or free) was 0.5 ug/mL. Intra-assay imprecision was <4.0% and inter-assay imprecision averaged <6.0% (n=20, at three levels).

2.4. Data analysis

CBZ, free CBZ, CBZ-EPO, and free CBZ-EPO clearance—Given that oral bioavailability could not be calculated from this population pharmacokinetic approach, we calculated apparent oral clearances (Cl) for total and free CBZ and CBZ-EPO.

$$\text{Drug Cl} = \text{carbamazepine daily dose (mg/kg)} / \text{serum drug concentration (ug/mL)}$$

Clearances were compared between different stages of pregnancy: nonpregnant (preconception or >6 weeks post-partum), first trimester (<14 weeks GA), second trimester (14–28 weeks GA), and third trimester (>28 weeks GA). For those who were already pregnant at enrollment, baseline (nonpregnant) clearances were calculated from postpartum samples collected from non-lactating women at more than 6 weeks following delivery. To investigate the change in clearance, two methods were used: 1) Clearances were compared for all measurements of each compound separated by stage of pregnancy using single-factor analysis of variance (ANOVA). 2) For verification of differences identified with ANOVA, Wilcoxon was used to compare clearances between baseline and each trimester for each woman and between trimesters. For patients who had more than one serum measurement in a trimester, the median measurement was used for comparison. An adjustment term was used for hours post dose as the time the sample was drawn was not standardized. A Bonferroni correction was used for multiple comparisons to determine significance.

Additionally, CBZ and free CBZ-EPO fractions were compared between nonpregnant baseline and each trimester and between each trimester, using single-factor analysis of variance (ANOVA).

2.5. Analysis of CBZ therapeutic drug monitoring and seizure frequency

For patients for whom adequate baseline information about seizure frequency and CBZ concentrations were available, we examined the association between CBZ (total and free, and –EPO) levels and seizure frequency. For this study, seizures with alteration of awareness were examined due to clinical relevance for medication adjustment.

Ratio of measured concentration to baseline concentration was calculated for each measurement (for total and for free CBZ). As ratio to baseline of less than 0.65 was previously found to correspond to an increased risk of seizures in patients on LTG and a variety of AEDs, data was examined using ratio to baseline of 0.65 or less as a hypothetical risk for increased seizures [2,14]. For each month of participation in the study, we coded the relative frequency of all types of seizures as 1 if the frequency was greater than the baseline monthly frequency (averaged over the previous non-pregnant 12 months) and 0 otherwise. Drug concentrations during months with increased seizure frequency were compared to serum concentrations of months with no increase in seizure frequency.

In addition, receiver operating characteristic (ROC) curves were constructed for each compound. Reduction of the ratio to baseline below some threshold was viewed as a positive test for diagnosing increased seizure frequency. The ROC curve was obtained by plotting true-positive versus false-positive rates and examined for any threshold ratio to baseline with high sensitivity and specificity (>75%).

3. Results

Overall 36 pregnancies involving 32 women treated with CBZ during pregnancy were enrolled in the study. A total of 17 pregnancies in 14 women had three or more blood measurements during two or more stages of pregnancy or non-pregnant baseline and included in the present analyses. Two pregnancies in two women were excluded from further analyses because they were being treated with interacting concomitant medications. Fifteen pregnancies in 12 women, encompassing 150 serum samples, were used for clearance analyses (see Figure 1). If a woman had more than one sample within 24 hours, the median was chosen. Characteristics of patients in study are shown in Table 1. Details of patients' seizure types and epilepsy etiology are shown in Table 2.

3.1. Change in Clearance

There was no significant change in clearances for total or free CBZ or total or free CBZ-EPO using ANOVA (see Figure 2).

Pair-wise comparison of the median clearances for each time period and at baseline found a decrease in clearance of free CBZ from baseline to trimester 1 ($p=0.03$), but did not remain significant after Bonferroni correction (threshold of significance $p<0.05$ prior to Bonferroni correction, and $p<0.004$ after Bonferroni correction); comparisons for total CBZ, and for total and free CBZ-EPO did not reveal significant changes between any time point.

ANOVA comparison of time periods showed a significant increase in the free CBZ fraction over time in pregnancy, from 23% at baseline to 32% in the third trimester ($p=0.008$) (Figure 3). There was a trend towards increase in free CBZ-EPO fraction from baseline to the first trimester (56% to 71%) but was not significant.

3.2. Seizure control and drug levels

Prospective and complete seizure tracking was available in nine women with epilepsy for analysis of seizure frequency on CBZ monotherapy. Of those nine, three women (33%) were seizure-free during the 12 months prior to pregnancy (and remained seizure free throughout pregnancy). Seizures with alteration of consciousness were examined due to clinical relevance. Two women (22%) had increased seizure frequency during the overall pregnancy. Three had fewer seizures than at baseline, and four had stable seizure frequency. Of the seven women with a history of generalized seizures, only one had generalized seizures during pregnancy.

Ratio of measured concentration to non-pregnant baseline concentration was calculated for each measurement (for total and for free CBZ and CBZ-EPO) for the six women with seizure data and multiple serum measurements during pregnancy and at baseline. Only one patient had increase in seizure frequency corresponding to total CBZ ratio to baseline <0.65 . This occurred at patient's nadir of total CBZ ratio to baseline 0.4 at delivery. No patient had a free CBZ ratio to baseline <0.65 . There were nine measurements (in three women) with free CBZ ratio to baseline <1 , however this was not predictive of an increase in seizure frequency.

Five women had total CBZ-EPO concentrations below baseline, and four women had free CBZ-EPO concentrations below baseline, however the nadirs of total and free CBZ-EPO did not correspond to months with increased seizures. Receiver operating characteristic (ROC) curves for each compound using ratio to baseline cutoff of 0.65, and additionally examined using cutoffs of 0.5, 0.6, 0.7, 0.8, 0.9, and 1.0, found no ratio to baseline with both high sensitivity and high specificity (75%).

4. Discussion

CBZ remains an important medication for women with epilepsy during pregnancy, and is one of the lower teratogenic options in many countries internationally. While current AAN Practice Parameter guidelines are to consider therapeutic monitoring of CBZ during pregnancy [1], TDM may not be feasible in all clinical settings. The current results do not support therapeutic drug monitoring of CBZ during pregnancy, which if found to be unnecessary in larger future studies has the potential to make CBZ a more favorable choice for women of childbearing age in areas where TDM is not possible.

Free CBZ is more clinically relevant than total CBZ, as only the free portion crosses the blood-brain barrier. Similarly, only free CBZ crosses the placental barrier and is more clinically relevant for fetal exposure [17]. The results from this small prospective cohort showed a significant increase in the free CBZ fraction throughout pregnancy, with a concomitant trend toward a decrease in clearance of free CBZ from baseline to early pregnancy, although not statistically significant after Bonferroni correction factor.

This study did not demonstrate a significant change in the clearance of total CBZ or free or total CBZ-epoxide throughout pregnancy. This finding is consistent with findings from prior studies [9,10,11,12,13], which have not consistently shown an increase in clearance, and in accordance with the largest study to date, which demonstrated little change for total and free CBZ[12]. This outcome provides a plausible explanation for the finding of the recent EURAP study that women on CBZ had the lowest rate of dosage increase or augmentation with a second AED during pregnancy compared to VPA, PB, and LTG. The clearance of CBZ and CBZ-10,11-epoxide shows minimal change during pregnancy, and there is evidence of an increase in the free drug. In combination, this would potentially provide protection from seizure worsening in women treated with CBZ. This is in contrast to AEDs in which clearance changes significantly, such as LTG in which total and free clearance increases significantly throughout pregnancy [2].

This study did not show a relationship between low total or free CBZ or total or free CBZ-EPO concentrations and increased seizure frequency. Given the limitations of pharmacokinetic research in pregnant human subjects including the need to limit the volume of blood drawn, weekly or more frequent sampling such as that used in traditional pharmacokinetic research is not possible. Other studies of other AEDs using the same design and similar frequency of sampling have found a relationship between increased seizures and lower ratio to baseline concentrations [2,15], implying that even without weekly sampling true effects could be detected by this method which mirrors typical clinical practice.

The limitations of the current study, including small size, point to the need for future large studies with more formal pharmacokinetic monitoring.

5. Conclusions

This study provides additional characterization of pharmacokinetic alterations during pregnancy of total and free CBZ, and especially of total and free CBZ-EPO. Due to the lack of change in total or free CBZ or CBZ-epoxide clearance and the absence of effect of serum concentrations on seizure control, CBZ may be a particularly favorable treatment option in women with focal seizures during pregnancy when limited resources dictate that therapeutic drug monitoring is not accessible or affordable. Confirmation of these findings in a larger prospective, multicenter study is warranted prior to definitive recommendations regarding the utility of therapeutic drug monitoring of CBZ during pregnancy.

Acknowledgments

Funding supported by an NIH Specialized Center of Research 5P50 MH68036 (ZNS, DJN, PBP, JCR), NINDS U01NS038455 (PBP, ZNS, MLN, BK), 2U01 NS38455, (PBP), and National Center for Research Resources NCRR M01-RR00039.

References

1. 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. *Neurology*. 2009; 73:142–149. [PubMed: 19398680]
2. Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in Pregnancy: Clearance, Therapeutic Drug Monitoring, and Seizure Frequency. *Neurology*. 2008; 70:2130–2136. [PubMed: 18046009]
3. International League Against Epilepsy. [Accessed 2/1/13] Worldwide AED Database. Available at: <http://www.ilae.org/Visitors/Centre/AEDs/index.cfm>
4. Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology*. 2012; 78:1692–9. [PubMed: 22551726]
5. Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol*. 2011; 10:609–17. [PubMed: 21652013]
6. 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 Mar; 12(3): 244–52. [PubMed: 23352199]
7. Pennell PB. Antiepileptic Drug Pharmacokinetics during Pregnancy and Lactation. *Neurology*. 2003; 61(Suppl 2):S35–S42. [PubMed: 14504308]
8. Leppik IE, Rask CA. Pharmacokinetics of Antiepileptic Drugs During Pregnancy. *SeminNeurol*. 1988; 8(3):240–6.
9. Yerby MS, Friel PN, Miller DQ. Carbamazepine Protein Binding and Disposition in Pregnancy. *Ther Drug Monit*. 1985; 7:269–273. [PubMed: 4049462]
10. Dam M, Christiansen J, Munck O, et al. Antiepileptic drugs: metabolism in pregnancy. *ClinPharmacokinet*. 1979; 4:53–62.
11. Battino D, Binelli S, Bossi L, et al. Plasma Concentrations of Carbamazepine and Carbamazepine 10,11-Epoxide During Pregnancy and After Delivery. *ClinPharmacokinet*. 1985; 10:279–284.
12. Tomson T, Lindbom U, Ekgvist B, et al. 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. [PubMed: 8112234]
13. Yerby MS, Friel PN, McCormick K. Antiepileptic drug disposition during pregnancy. *Neurology*. 1992; 42,4(Suppl 5):12–16. [PubMed: 1574166]

14. Harden CL, Meador KJ, Pennell PB, et al. Practice Parameter Update: Management issues for women with Epilepsy—Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009; 73:133–141. [PubMed: 19398681]
15. Reisinger TL, Newman M, Loring DW, et al. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. *Epilepsy Behav*. 2013; 29:13–18. [PubMed: 23911354]
16. Battino D, Tomson T, Bonizzoni E, et al. Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry. *Epilepsia*. 2013; 54(9):1621–7. [PubMed: 23848605]
17. Blackburn, ST. Maternal, fetal, and neonatal physiology: a clinical perspective. 4. Maryland Heights: Elsevier Saunders; 2013.

Highlights

- Total and Free CBZ and CBZ-EPO clearances do not change significantly throughout gestation
- The free fraction of CBZ does increase during pregnancy
- Changes in seizure frequency are not associated with lower concentrations of total or free CBZ or CBZ-EPO

Figure 1.

Flow diagram of women enrolled in the study and information used for data analysis

Clearance by stage of pregnancy

$P > 0.05$ for all compounds by ANOVA.

α $p = 0.03$ by Wilcoxon (level of significance 0.004 after Bonferroni correction)

Figure 2.

Clearance of compounds throughout pregnancy (95% confidence intervals shown with error bars)

Figure 3.
Free Fraction of CBZ and CBZ-EPO (95% confidence intervals shown with error bars)

Table 1

Clinical characteristics of women included in the analysis of CBZ clearances and free fractions

Total number of patients	12
Total number of pregnancies	15
Racial distribution (% of total)	
White	7 (58.3%)
African-American	4 (33.3%)
Native American	1 (8.3%)
Mean age (range)	30.93 (21–42)
Mean gestational age at delivery (range), wks	37.2 (30.9–40.7)
History of generalized tonic-clonic seizures	8 (66.7%)
Seizure-free (>1 year) prior to pregnancy	3 (25%)
Reason for treatment	
Localization-related epilepsy	10/12 (83.3%)
Juvenile myoclonic epilepsy	1/12 (8.3%)
Movement disorder	1/12 (8.3%)

Table 2

Details of epilepsy and movement disorder for individual subjects included in the analysis

Patient	Classification	Etiology	Seizure types	EEG data	MRI findings	Laterality
A*	Temporal Lobe Epilepsy	MTS	CPS	Right frontotemporal sharp waves and focal slowing	Status-post right anterior temporal lobectomy	Right
B	Temporal Lobe Epilepsy	MTS	SPS; CPS; SGS	Left temporal and occipital spikes and sharp and slow wave discharges	Left MTS	Left
C*	Temporal Lobe Epilepsy	Unknown	SPS; CPS; SGS	Left temporal sharp and slow wave discharge and focal slowing	Normal	Left
D*	Temporal Lobe Epilepsy	MTS	SPS; CPS; SGS	Normal by report	Right MTS	Right
E	Movement disorder	Unknown	Paroxysmal kinesogenic dyskinesia	Normal EEG	Not performed	Not applicable
F	Temporal Lobe Epilepsy	MTS	CPS; SGS	Ictal: Left anterior temporal lobe seizure onsets	Left MTS	Left
G	Frontal Lobe	Structural, malformation of cortical development	CPS	Ictal: Left frontotemporal spikes evolving to generalized spike wave discharges with postictal slowing	Left frontal cortical dysplasia	Left
H	Frontal Lobe	Structural, stroke	CPS; SGS	Normal EEG	Left>Right frontal encephalomalacia	Bilateral
I	Temporal Lobe Epilepsy	MTS	CPS; SGS	Normal EEG	MTS	Left
J	Juvenile Myoclonic Epilepsy	Presumed Genetic	GTC; myoclonic	Generalized 3Hz sharp and slow wave discharges	Not performed	Generalized
K	Localization related (nonclassified)	Unknown	CPS	Normal EEG	Normal	Unknown
L	Temporal Lobe Epilepsy	Unknown	SPS; CPS; SGS	Left temporal polymorphic delta slowing	Normal	Left