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Differential Effects of Antiepileptic Drugs on Neonatal Outcomes

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Abstract

Offspring of women with epilepsy (WWE) on AEDs are at increased risks for major congenital malformations and reduced cognition. They may be at risk for other adverse neonatal outcomes. WWE on carbamazepine (CBZ), lamotrigine (LTG), phenytoin (PHT), or valproate (VPA) monotherapy were enrolled in a prospective, observational, multicenter study of the neurodevelopmental effects of AEDs. The odds ratio for small for gestational age (SGA) was higher for VPA vs. PHT, VPA vs. LTG, and CBZ vs. PHT. Microcephaly rates were elevated to 12% for all newborns and 12-months-old, but normalized by age 24-months. Reduced Apgar scores occurred more frequently in the VPA and PHT groups at 1 minute, but scores were near normal in all groups at 5 minutes. This study demonstrates increased risks for being born SGA in the VPA and CBZ groups, and transiently reduced Apgar scores in the VPA and PHT groups. Differential risks amongst the AEDs can help inform decisions about AED selection for women during childbearing years.

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Keywords

Epilepsy; seizures; Antiepileptic drugs; Pregnancy; Neonatal; microcephaly; Small for Gestational Age (SGA); Apgar; Observational cohort study

Introduction

Epilepsy is one of the most common neurological disorders affecting approximately 50 million people according to the World Health Organization [1]. Over one-fourth are women of childbearing potential. Although the vast majority of children born to women with epilepsy (WWE) on antiepileptic drugs (AEDs) are healthy, studies have reported increased risks for several adverse outcomes. Evidence necessary to direct care of WWE planning and during pregnancy is inadequate [2]. Findings from research that define differential risks amongst the AEDs prescribed during pregnancy are critical to allow physicians and patients to make informed choices to mitigate risks to the developing baby while maintaining seizure control. Much of the literature has concentrated on risk for major congenital malformations and poor neurodevelopmental outcomes, with consistent findings that the risk is greatest for valproate (VPA) monotherapy and AED polytherapy [2-4]. It is less clear whether there are increased risks for adverse neonatal outcomes, including being born small for gestational age (SGA), microcephaly, and low Apgar scores, and if the amount of risk varies amongst the different AEDs [2].

SGA newborns are at risk for stillbirth, impaired thermoregulation, hypoglycemia, and long term sequelae including impaired neurodevelopment and cardiovascular diseases and diabetes in adulthood [5-8]. Apgar scores provide a standardized assessment for reporting the neonate's need and response to resuscitation [9]. If less than 7 at one minute, resuscitation is considered, and low 5-minute scores are associated with increased risk of cerebral palsy and seizures [9,10]. Neonatal microcephaly is commonly associated with subsequent neurodevelopmental delay.

Critical data are lacking or conflicting regarding neonatal outcomes in children born to women with epilepsy [2]. This secondary analysis of a prospective, observational, multicenter study that enrolled pregnant women with epilepsy on different AEDs was undertaken to detect differential risks among the AEDs that could inform clinical practice and be incorporated into decision making regarding AED selection in women of childbearing age.

METHODS

Standard Protocol Approval, Registrations, and Patient Consents

The Institutional Review Board of each clinical site approved the study. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent for research was obtained from all women participants.

Participants

Between 1999 and 2004, pregnant women with epilepsy were enrolled who were taking a single AED (either CBZ, LTG, PHT, or VPA) at time of conception to enrollment in a prospective, observational, multicenter study across 25 centers in the United States and United Kingdom. This Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study was primarily designed for a comparison of neurodevelopmental outcomes at age 6 years after in utero exposure to each of these different AEDs. Exclusion criteria included

additional AEDs at any time during the pregnancy including prior to enrollment, pregnancy > 20 weeks gestational age (GA), history of drug or alcohol abuse, IQ <70, history of AIDS or syphilis, other major medical illness including diabetes mellitus, progressive cerebral disease, taking other teratogens, and poor compliance with prenatal care. No women were enrolled for more than one pregnancy. This report focuses on the neonatal findings of SGA, head circumference (HC), and Apgar scores in this cohort of mother-child pairs.

SGA

SGA was defined as birthweight at 10^{th} percentile or less, conditional on GA and gender [11,12]. GA was determined by the woman's obstetrician and took into consideration first day of last menstrual period and ultrasound results. A logistic regression model was fit to the data with SGA status (yes/no) as outcome. Covariates initially included in the model were AED group, standardized pregnancy average AED dose, and GA at birth. AED dose was standardized relative to ranges observed within each group: 100 × (observed dose − minimum dose)/(range). Using a backwards selection strategy, a number of additional covariates were considered including: chronic hypertension, convulsion frequency during pregnancy, socio-economic status (SES), pregnancy hypertension, gestational diabetes, seizure type, prenatal folate use, any alcohol during pregnancy and any tobacco during pregnancy. Using the backwards selection strategy, a final model was obtained which includes AED group, GA at birth, tobacco during pregnancy and gestational diabetes. This same model was obtained using a manual strategy in which covariates were added to the model one by one and were kept in the model if significant at the .05 level. The model was also applied to the subgroup of neonates born full term (38 – 42 weeks GA).

Weight was measured by the pediatrician at later ages, as per local standard clinical practice. Outside records were obtained for recording weights at age 24 months and age 36 months and were compared to the population norms by gender [12].The frequency of weight less than the 10^{th} percentile at ages 24 months and 36 months were analyzed by AED group utilizing Fisher's exact test.

Microcephaly

Head circumference was measured at birth by the labor and delivery medical team and by the pediatrician at later ages, as per local standard clinical practice. Outside records were obtained for recording of HC. Details were not available in the records as to type and subdivision of the measurement tape used, or if a second measurement was obtained. Microcephaly was defined as less than third percentile for gender [13]. A logistic regression model was fit to the data at age 0 months and at 12 months; response variable was HC less than third percentile (Yes/No). Covariates included AED group, gender, GA at birth, and mother's HC. Subsequent HC measurements at ages 24 and 36 months were also analyzed. Secondary analysis was performed with least squares adjusted means and pairwise comparisons from an ANCOVA model controlling for AED Group and average of mother's and father's HC. The model was also applied to the subgroup of neonates born full term (38 – 42 weeks GA).

Apgar scores

Standardized Apgar scores are measured at one and five minutes; scores of 7-10 are considered normal [9,10]. The percentages of neonates that had an Apgar score less than 7 at 1 minute and at 5 minutes were compared across groups using Fisher's exact test.

Association with cognitive outcomes at age 3

Regression analyses were performed to investigate the relationship between neurodevelopmental outcomes and the neonatal findings of microcephaly, SGA, and low Apgar scores, with age three IQ as the outcome variable. Indicators of SGA, microcephaly, and low APGAR scores were each added individually to a model, described in detail in our previous report [3], which included AED group, maternal IQ, maternal age, GA, pregnancy average AED dose and preconception folate as predictors.

RESULTS

Participants

The NEAD study enrolled 329 women with epilepsy during pregnancy prior to 20 weeks GA, producing 311 live births. Six mothers had twins. Mean GA of enrollment was 17.5 weeks, with a range of 3-19 weeks. For GA determination, 97.7% of the women had an ultrasound recorded in the database. Of the 311 neonates, 3 were not included in the SGA analysis due to missing birthweight (two in the LTG group, one in the CBZ group). One-hundred and six of the neonates were enrolled from antenatal clinics in the UK and were previously included in analysis of birthweight in comparison to healthy controls [14]. The distribution of the mother-child pairs for each AED group and demographics are detailed in Table 1. Five additional neonates were excluded from the APGAR analysis for missing data. HC data was available on 226 neonates, with reduced numbers at later ages (Table 5).

Primary analyses were conducted with all twins included. However, to check sensitivity of results to the inclusion of twins, one twin from each pair was randomly omitted from the analyses and results did not substantively change. Sixteen children had major congenital malformations, and none had identified chromosomal abnormalities. In primary analyses, children with malformations were included. To check sensitivity of results to inclusion of these children, analyses were re-run with these 16 children excluded and results did not change substantively.

SGA

In the initial model for SGA containing standardized pregnancy average AED dose, AED group, and GA, the only predictors found to be significant were AED group (p=0.0408) and GA (p=0.0056). When additional covariates were examined as possible predictors of SGA, only two were significant: ‘any tobacco during pregnancy’ (p=0.0002) and ‘gestational diabetes’ (p=0.0349). Other covariates examined were non-significant. Using a backwards selection strategy, a final logistic regression model was obtained which included AED, GA, tobacco use, and gestational diabetes. Both gestational diabetes and tobacco use are associated with greater odds for being SGA, and increased GA is associated with decreased odds of being SGA.

Birth weights of 308 neonates were analyzed (Table 1), and 27/308 (8.76%) met criteria for SGA. No unexposed comparison group was available in this study (newborns of women with epilepsy on no AEDs). The comparison was made to the general population, and SGA was defined as10th percentile or less, conditional on GA and gender. Percent of neonates born SGA by AED monotherapy group were CBZ (12.9%), LTG (4.1%), PHT (3.6%) and VPA (14.5%) (Figure 1). Controlling for the covariates tobacco use, gestational diabetes, and GA, several AED comparisons were significant (Table 2). SGA was more common for VPA>PHT, VPA>LTG, and CBZ>PHT. CBZ>LTG was marginally significant. Three of the SGA neonates were a twin, but none from the same pregnancy. Of the SGA babies, 6 (22%) were preterm (< 37 weeks GA). Of non-SGA babies, 21 (8%) were preterm, indicating that preterm babies were more likely to be SGA (p-value=.02; Fisher’s Exact

test). The percentage of preterm babies did not differ across AED groups (p-value=.60; Fisher's Exact test).

When the analysis of birth weights was limited to the infants born full-term (38 - 42 weeks GA) (n=239), significant differences between the monotherapy groups occurred. The percent of full-term newborns that were SGA by monotherapy group were CBZ (11.5%), LTG (3.6%), PHT (0%), and VPA (7.7%) (Table 3).

The finding of weight < 10th percentile differing by AED group persisted at age 24 months with CBZ (19.2%), LTG (3.1%), PHT (8.3%), and VPA (16.1%); the differences by AED group disappeared by 36 months and each AED group demonstrated normal weight ranges (Table 4).

Head circumference

The subset of neonates included in the microcephaly analysis is listed in Table 5 by AED group and age of analysis. For all AED groups combined, 12-13% met criteria for microcephaly at birth and 12 months, but only 3% at 24 months and 2% at 36 months.

A logistic regression model was fit to the data at birth and at age 12 months. Response variable was HC Less than 3rd percentile (Yes/No). At birth, AED group is not significant, although gender (p=0.0497) and GA (p<0.0001) are significant covariates. At age 12 months, AED group is significant (p=0.0131) and gender and GA are not significant covariates. CBZ followed by VPA had the highest percentage of microcephaly in neonates and 12 month old infants (Table 5). When the analysis was limited to full-term neonates (38 – 42 weeks GA), microcephaly rates were similar to findings of the entire cohort at 12, 24, and 36 months of age, except that they were lower at birth (6%) (Table 6). AED group is significant at age 12 months with similar findings of highest percentage of microcephaly rates in the CBZ followed by the VPA group (Table 6).

Newborn head circumference was correlated with the average of the parents' head circumferences (pearson correlation=0.16; p-value=.05). A positive correlation was observed also at 12 and 36 months. At 24 months, the correlation with parental head circumference was marginally significant (pearson correlation = 0.17, p-value=.08).

Secondary analysis controlling for AED Group and average maternal HC revealed that both the CBZ group and the PHT group had a smaller HC than the LTG group at birth (p=0.0250 and p=0.0138, respectively), but only the CBZ group remained smaller compared to the LTG group at age 12 months old (p=0.0019). No other group differences were found, including comparisons at ages 24 and 36 months. There was a fair amount of missing data in the microcephaly analysis at ages 24 and 36 months; results were similar when the analysis was restricted to the sample with HC data available at each time point.

At each age, we compared HC means by SGA status. For newborns, SGA babies have significantly smaller HC (p=.0034; ANOVA model), but at ages 12 and 24 months, there were no significant differences between SGA and non-SGA babies in HC.

Apgar Scores

The percent of neonates that had a 1-minute Apgar score less than seven differed by AED group (Fisher's exact test; p=0.0015), poorest for VPA and best for LTG (Table 7). However, AED differences disappeared by the 5-minute Apgar scores (p=0.1632). The difference between the percentages with low Apgar scores did not differ significantly by SGA status (p=.54; Fisher's Exact test).

Association with neurodevelopmental outcomes

Regression analyses using the model demonstrated that none of the neonatal findings of SGA, low Apgar scores, or microcephaly at birth negatively impacted 3-year-old neurodevelopmental outcomes. SGA was not associated with lower age 3 cognitive outcomes, using least squares adjusted means from a regression model with age 3 IQ as outcome and controlling for AED group, maternal IQ, maternal age, gestational age at birth, pregnancy average AED dose and folate. Newborn head circumference was not associated with higher cognitive outcomes at age 3 (linear regression model controlling for AED group, maternal head circumference, maternal age, maternal IQ, gestational age, dose and folate). Similarly, head circumference at ages 1, 2 and 3 were also not associated with cognitive outcomes at age 3. When Apgar scores at 1 and 5 minutes were added to the linear regression model with age 3 IQ as outcome and maternal IQ, AED group, maternal age, dose, gestational age and folate as predictors, none of the Apgar scores were associated with cognitive outcomes at age 3.

DISCUSSION

The NEAD study prospectively enrolled pregnant women with epilepsy prior to 20 weeks GA who were taking CBZ, LTG, PHT, or VPA monotherapy from multiple centers across the US and UK. The present analyses examined neonatal outcomes that may deserve further investigation. These outcomes are considered secondary outcomes in the NEAD study. This study was not powered for or designed to control for multiple statistical testing associated with secondary outcomes. Because of the design of the initial NEAD study, detailed information was available on key covariates including epilepsy and seizure types, number of convulsive seizures, detailed health history including for HTN, tobacco use, concomitant medications, AED type and dose. There is indication that VPA and CBZ are associated with higher risk for SGA compared to PHT and LTG. The rate of SGA for all AED monotherapy groups combined in this study was not elevated, and the differential findings highlight that the risk for SGA is not necessarily an all-inclusive effect of AEDs. The overall rate of SGA, 8.8%, is likely less than 10% given the exclusion criteria for women with other chronic diseases, alcohol or drug abuse, and poor compliance with prenatal care. Certain AEDs may contribute to SGA by decreasing uterine blood flow or via myometrial effects limiting fetal growth. The impact of being born SGA on immediate and long-term health can be substantial [5-7,15]. Additionally, fetal growth restriction is a common antecedent of stillbirth [8]. The first outcomes report from this NEAD cohort included a stillbirth rate of 2.4% [16]; in contrast, the mean stillbirth rate in the US is approximately 0.6% and in the UK is 0.35% [17,18].

The high rates of microcephaly (defined as <3%ile) for all AED groups at birth and age 12-months of 12-13% are of interest and potentially concerning. However, rates of microcephaly at ages 24-months and 36-months are similar to population rates for microcephaly, and the clinical implications for early microcephaly are unclear. HC population norms are given for birth regardless of GA, and thus it is not surprising that GA is a significant covariate for microcephaly at birth but disappears by age 12-months. The CBZ monotherapy group has the highest percentage of neonates and 12-month-old infants meeting criteria for microcephaly, followed by the VPA monotherapy group, similar to previous reports [19,20], but the prior studies did not follow the children past 18 months of age. The rates of microcephaly in the NEAD cohort attenuate substantially even for the CBZ and VPA monotherapy group by age-24-months (Table 5).

Animal studies have demonstrated that many AEDs, including PHT and VPA, cause apoptotic neurodegeneration in the developing rat brain when delivered to either the fetus or the rat pups by intraperitoneal injection, producing plasma concentrations similar to those

used for seizure control in humans [21]. The authors propose that this mechanism contributes directly to reduced brain mass as well as cognitive impairment [21]. However, these findings should be replicated in animal studies utilizing oral exposure to confirm relevance to oral exposure in human pregnancies. A similar apoptotic effect has not been demonstrated for CBZ monotherapy. The similar vulnerability for SGA and microcephaly for both the neonates exposed to CBZ and to VPA in utero raises the possibility that another shared mechanism contributes to these findings, such as inhibition of cell growth and development. Alternatively, some AEDs could be associated with systemic as well as neuronal apoptotic effects in humans.

The reduced 1-minute Apgar scores for VPA and PHT are of unclear consequence given that Apgar scores normalize by 5 minutes [22]. It is possible that a heightened scrutiny of neonates born to WWE could influence the initial rating. The improvement is reassuring, but knowledge of lower 1-minute-Apgar scores in the VPA and PHT groups can help guide the delivery team to appropriately prepare for the immediate neonatal period. Detailed information about interventions between 1 and 5 minutes was not available for this cohort, such as blow-by oxygen delivery, suction, or assisted ventilation.

Previous detailed analysis of the literature concluded that women with epilepsy taking AEDs probably have an increased risk of SGA of about twice the expected rate compared to healthy controls, but there is little data for specific AED comparisons [2]. Some studies do not show a significantly increased risk of SGA for WWE not on AEDs, implying that *in utero* AED exposure may be a key contributor to lower birth weights [23,24]. Apgar scores at 1-minute or at 5-minutes were not lower in neonates of WWE in most but not all studies [2,24]. Several recent studies raised further concern that there are increased neonatal risks [25,36]. In contrast to other studies, an analysis of the Medical Birth Registry of Norway, allowing utilization of an unselected population of WWE on AEDs and not on AEDs, reported that compared to a control group of non-epilepsy births, the odds ratio for SGA was higher for neonates of WWE on no AED and on AEDs (both OR 1.2, $p<0.05$)[25]. Limitations of the prior published studies include retrospective data collection, missing data, and use of ICD-9 codes and national databases or discharge summaries to select patient populations and collect data. Studies in different countries reflect a variety of neurological practices and often have fewer than expected women with epilepsy on AEDs and different AEDs. Data from these prior studies were not sufficiently detailed to determine AED dose, epilepsy type, and seizure frequency during pregnancy. A strength of the present study is a relatively uniform population of women with active epilepsy requiring ongoing treatment, and perhaps slightly more uniform level of severity of disease since all women were on AED monotherapy. This allows for more direct comparisons between the different AED monotherapy groups studied. The prospective, detailed uniform data collection, including factors that can affect the neonatal outcomes of interest, provided the opportunity to incorporate key covariates into the analysis models. Most covariates were not significant, some of which differs from prior studies but is likely due to the fact that the women enrolled in the NEAD study were fairly uniform without a high prevalence of these other risk factors, and they may have had fewer convulsive seizures, or different seizure types, than the population-based studies.

Limitations of this study include the number of newborns with missing data, especially for the HC analysis. Many of the NEAD mothers gave birth at outside hospitals different from the site principal investigator's primary hospital, and the protocol did not include the investigator or coordinator going to the newborn nursery to do an exam. Similarly, physical examination findings at later ages were obtained from pediatrician records. HC was often missing from the medical charts, especially in the VPA group. It is possible that differences between AEDs may have been detected at later ages with more subjects in each group.

Future studies designed to identify adverse neonatal outcomes and differentiate potential contributory factors should include other AEDs that are now prescribed in women of childbearing age [27], AED polytherapies given the potential synergistic impact on adverse outcomes, women with epilepsy not on AEDs, and a healthy control group with similar baseline demographics. More detailed data collection from the obstetric labor and delivery suites through the neonatal hospital stay could provide additional insight into factors that could be modified to reduce or better manage adverse neonatal outcomes. Analytical models should also take into account not only AED type and dose, but AED levels in the mother and the neonate at birth as a closer surrogate marker for fetal exposure, especially given that AED clearance can have substantial intraindividual and interindividual variability during pregnancy [28].

This analysis of neonatal outcomes from the NEAD study group demonstrates increased risks for SGA following in utero exposure to CBZ or VPA monotherapy, overall elevated rates of microcephaly at birth and 12 months-old, but normal rates by age 24-months-old, and transiently reduced Apgar scores following in utero exposure to VPA or PHT. Differential risks amongst the AEDs can help guide decisions about AED selection for women during childbearing years, as well as help inform management of their offspring in the neonatal period.

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APPENDIX

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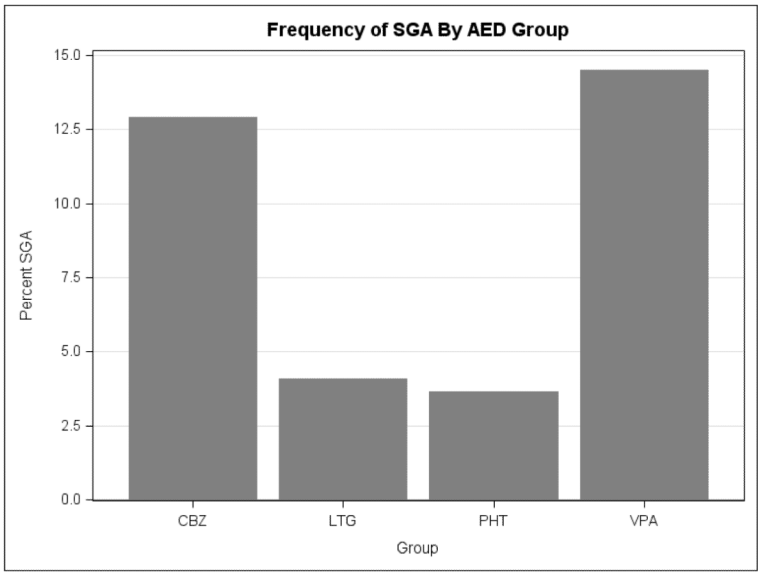

Figure 1.
Percent of newborns in each AED group that met criteria for Small for Gestational Age (<10th percentile). (CBZ = carbamazepine, LTG = lamotrigine, PHT = phenytoin, VPA = valproate).

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Table 1

Demographics for mothers of children included in the SGA analysis

Antiepileptic Drug	Carbamazepine	Lamotrigine	Phenytoin	Valproate	Total
Mothers (n)	92	97	52	61	302
Children (n)	93	98	55	62	308
Mean Maternal IQs (95% CI)	99.0 (95.5:102.6)	101.1 (97.7:104.4)	92.3 (87.7:97.0)	96.1 (92.4:99.7)	97.9 (96.1:99.8)
Mean Maternal Ages (95% CI)	30.2 (29.2:31.3)	30.0 (28.9:31.1)	30.5 (28.9:32.2)	28.3 (26.7:29.9)	29.8 (29.2:30.5)
Mean Dose[A] **mg/day (95% CI)**	779.0 (692.3:865.7)	448.1 (399.1:497.1)	399.7 (364.2:435.2)	1032.4 (877.2:1187.6)	N/A
Standardized Dose[B] **(95% CI)**	32.2 (28.4:35.9)	34.1 (29.9:38.3)	48.7 (43.5:53.9)	26.1 (21.6:30.6)	34.4 (32.1:36.7)
Gestational Age at Birth, weeks (95% CI)	38.5 (38.0:39.0)	39.3 (38.9:39.7)	38.6 (37.8:39.3)	39.2 (38.7:39.7)	38.9 (38.6:39.2)
Preterm Birth (< 37 weeks GA) n(%)	10 (11)	6 (6)	6 (12)	5(8)	27 (9)
Gender = Female n (%)	55 (60)	51 (52)	28 (54)	26 (42)	160 (53)
Preconception Folate n (%)	54 (59)	58 (60)	21 (40)	39 (64)	172 (57)
Chronic hypertension n (%)	0 (0)	3 (3)	0 (0)	1 (2)	4 (1)
Gestational hypertension n (%)	5 (5)	5 (5)	3 (6)	4 (7)	17 (6)
Gestational Diabetes n (%)	1 (1)	5 (5)	5 (10)	1 (2)	12 (4)

Antiepileptic Drug	Carbamazepine	Lamotrigine	Phenytoin	Valproate	Total
Alcohol use[C] during pregnancy n (%)	8 (9)	8 (8)	3 (6)	5 (8)	24 (8)
Tobacco use during pregnancy n (%)	14 (15)	8 (8)	6 (12)	9 (15)	37 (12)
Type of Epilepsy					
Localization Related Epilepsy[D] n (%)	81 (88)	50 (52)	40 (77)	12 (20)	183 (61)
Idiopathic Generalized Epilepsy[D] n (%)	6 (7)	39 (40)	8 (15)	43 (70)	96 (32)
Uncertain if focal or generalized[D] n (%)	5 (5)	8 (8)	4 (8)	6 (10)	23 (8)
Convulsive Seizures					
Occurrence of convulsions during pregnancy[E] n(%)	10 (12.20)	18 (21.18)	9 (18.37)	14 (23.33)	51 (18.48)
Race and Ethnicity					
Caucasian n (%)	75 (82)	85 (88)	30 (58)	53 (87)	243 (80)
Black n (%)	6 (7)	1 (1)	5 (10)	1 (2)	13 (4)
Hispanic n (%)	6 (7)	6 (6)	16 (31)	3 (5)	31 (10)
Other n (%)	5 (5)	5 (5)	1 (2)	4 (7)	15 (5)

[A] Average dose for pregnancy.

[B] See Methods for description of how dosages were standardized.

[C] Any alcohol use during pregnancy (yes/no)

[D] Epilepsy types: Localization Related (includes cryptogenic and symptomatic); Idiopathic Generalized (includes absence, juvenile myoclonic, genetic, and other idiopathic generalized not otherwise classified); Uncertain if focal or generalized (all with history of generalized tonic clonic seizures).

[E] Convulsions = number (%) of mothers that experienced convulsive seizures during pregnancy. Seizure frequency during pregnancy not reported for n=26 mothers.

Table 2

Comparison of AED groups for SGA births by Odds Ratio Estimates with 95% confidence limits. (VPA = valproate, CBZ = carbamazepine, PHT = phenytoin, LTG = lamotrigine)

AED Comparisons	Odds Ratio Estimate	95% Wald Confidence Limits for Odds Ratios	
VPA vs. CBZ	1.30	0.48	3.52
VPA vs. PHT	7.25	1.30	40.28
VPA vs. LTG	4.08	1.11	14.96
CBZ vs. PHT	5.58	1.06	29.34
CBZ vs. LTG	3.14	0.91	10.90
PHT vs. LTG	0.56	0.09	3.46

Table 3

Frequency by AED group of full-term neonates that met criteria for SGA (<10th percentile weight for GA and gender). (CBZ = carbamazepine, LTG = lamotrigine, PHT = phenytoin, VPA = valproate)

AED Group	n/N (%) < 10th percentile weight for GA and gender
CBZ	9/78 (11.5)
LTG	3/84 (3.6)
PHT	0/41 (0.0)
VPA	4/52 (7.7)
ALL	16/255 (6.3)
p-value for differences across groups (Fisher's Exact Test)	0.0502

(N = number of entire cohort in this analysis; n = number of children that met criteria for SGA (<10th percentile weight for GA at birth and gender).

Table 4

Frequency by AED group of children <10th percentile weight, for age and gender, at 24 months and at 36 months. (CBZ = carbamazepine, LTG = lamotrigine, PHT = phenytoin, VPA = valproate)

AED Group	n/N (%) < 10th percentile weight for age and gender
	Age 24 months
CBZ	10/52 (19.2)
LTG	2/64 (3.1)
PHT	3/36 (8.3)
VPA	5/31 (16.1)
ALL	20/183 (10.1)
p-value for differences across groups (Fisher's Exact Test)	0.0201
	Age 36 months
CBZ	3/63 (4.8)
LTG	6/68 (8.8)
PHT	3/45 (6.7)
VPA	1/44 (2.3)
ALL	13/220 (5.9)
p-value for differences across groups (Fisher's Exact Test)	0.541

Table 5

Frequency by age and AED group of microcephaly, defined as head circumference less than third percentile. (CBZ = carbamazepine, LTG = lamotrigine, PHT = phenytoin, VPA = valproate)

AED Group	Age=0 Months	Age=12 Months	Age=24 Months	Age=36 Months
	n/N (%) < 3rd Percentile			
CBZ	13/69 (19)	15/63 (24)	2/42 (5)	2/52 (4)
LTG	6/71 (9)	5/81 (6)	2/57 (4)	0/58 (0)
PHT	4/48 (8.)	3/47 (6)	0/35 (0)	1/40 (3)
VPA	4/38 (11)	7/40 (18)	1/29 (4)	0/42 (0)
ALL	27/226 (12)	30/231 (13)	5/163 (3)	3/192 (2)
p-value for differences across groups (Fisher's Exact Test)	0.26	0.007	0.68	0.32

(N = number of entire cohort in this analysis; n = number of children with microcephaly).

Table 6

Frequency by age and AED group of microcephaly, defined as head circumference less than third percentile, among infants born full term. (CBZ = carbamazepine, LTG = lamotrigine, PHT = phenytoin, VPA = valproate)

AED Group	Age=0 Months	Age=12 Months	Age=24 Months	Age=36 Months
	n/N (%) < 3rd Percentile			
CBZ	7/57 (12)	14/52 (27)	2/34 (6)	2/43 (5)
LTG	3/61 (5)	4/70 (6)	2/48 (4)	0/51 (0)
PHT	1/36 (3)	3/34 (9)	0/25 (0)	1/29 (3)
VPA	1/31 (3)	6/33 (18)	0/24 (0)	0/35 (0)
ALL	12/185 (6)	27/189 (14)	4/131 (3)	3/158 (2)
p-value for differences across groups (Fisher's Exact Test)	0.29	0.007	0.59	0.26

(N = number of entire cohort in this analysis; n = number of children with microcephaly).

Table 7

Apgar scores that were <7 by AED group. (CBZ = carbamazepine, LTG = lamotrigine, PHT = phenytoin, VPA = valproate)

Apgar at 1 minute < 7	**AED N (%)**				
	CBZ	**LTG**	**PHT**	**VPA**	**Total**
NO	82 (90)	93 (96)	43 (81)	48 (77)	266 (88)
YES	9 (10)	4 (4)	10 (19)	14 (23)	37 (12)
Total	91	97	53	62	303
Fisher's Exact Test: p=0.0015					
Apgar at 5 minutes < 7	**AED N (%)**				
	CBZ	**LTG**	**PHT**	**VPA**	**Total**
NO	90 (99)	97 (100)	51 (96)	60 (97)	298 (98)
YES	1 (1)	0 (0)	2 (4)	2 (3)	5 (2)
Total	91	97	53	62	303
Fisher's Exact Test: p=0.1632					