Fetal Growth and Premature Delivery in Pregnant Women on Anti-epileptic Drugs

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*****Dedicated to Dr. Autumn Klein, whose life was interrupted before she could complete this project for her patients**.**

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ABSTRACT

Objective: To evaluate the effects of epilepsy and antiepileptic drugs (AED) use during pregnancy on fetal growth and preterm delivery.

Methods: This study included singleton liveborns born to women enrolled in the North American Antiepileptic Drug Pregnancy Registry between 1997 and 2016. Data were collected prospectively through telephone interviews. The prevalence of preterm birth (<37 weeks) and small-for-gestational-age (SGA) among infants exposed prenatally to AED when used by women with epilepsy (WWE) or women without epilepsy (WWOE) was compared with that among infants unexposed to AEDs and born to WWOE. Multivariable log-binomial regression models were used to estimate relative risks (RR) and 95% confidence intervals (CI).

Results: The study population included infants born to 6,777 AED-WWE, 696 AED-WWOE, and 486 no-AED WWOE. The risk of prematurity was 6.2% for no-AED-WWOE, 9.3% for AED-WWE (RR 1.5, 95%CI: 1.0-2.1) and 10.5% for AED-WWOE (RR 1.5: 1.0-2.4). Prenatal exposure to AED in WWE and WWOE was associated with a mean lower birth weight of 110 and 136 grams, respectively, as compared to no-AED WWOE. The prevalence of SGA was 5.0% for no-AED-WWOE, 10.9% for AED-WWE (RR 2.0: 1.3-3.0) and 11.0% for AED-WWOE (RR 1.9: 1.2-2.9). Within users of AEDs in monotherapy, the prevalence of SGA ranged from 7.3% for lamotrigine to 18.5% for topiramate.

Interpretation: Women on AEDs during pregnancy, whether for epilepsy or for other neuropsychiatric indications, are at a higher risk of delivering prematurely and giving birth to SGA newborns. The risk may vary by drug.

INTRODUCTION

There are approximately one million women of reproductive age with epilepsy in the U.S.; 24,000 offspring are born to these women each year.[1] The prevalence of antiepileptic drugs (AED) prescriptions for women 15 to 44 years old increased significantly in the last decades, with over 4 million annual prescriptions written for epilepsy (20.7% of all AED prescriptions), mental illnesses such as mood disorders (47.9%) and chronic pain syndromes including neuropathies and migraine headaches (22.2%).[2] As a result, AEDs are taken by 0.4% of pregnant women just for epilepsy,[3] and an increasing number of patients are prescribed AEDs during pregnancy for other conditions.

Although the main concern regarding use of AEDs in pregnancy is their potential structural teratogenicity[4] and neurodevelopmental effects[5,6], there are other potential concerns. In the 1960s, case reports and small case series reported that women with epilepsy had a higher incidence of preterm delivery and neonatal complications, including delivering infants small for gestational age (SGA;<10th percentile for weight given gestational age at birth). However, these outcomes could be attributable to the disease or the treatments. Although most AEDs either do not affect weight or cause weight gain, some have been shown to cause weight loss in adults.[7-10] There is little information on the potential effects of AEDs in premature delivery and fetal growth.[11-16]

We used data from the North American AED (Antiepileptic Drug) Pregnancy Registry to estimate the risks of prematurity and of being SGA in infants whose mothers had taken AEDs either for epilepsy or for other indications during pregnancy, and to compare these risks with those in infants born to an unexposed comparison group.

METHODS

The North American AED Drug Pregnancy Registry is an ongoing cohort study of pregnant women who have taken AEDs at some point during her pregnancy .[17] Participants enroll by calling the registry. Three phone interviews are conduced; one at enrollment, one at 7 months of gestation, and one 8 to 12 weeks after the expected date of delivery. The computer-assisted interviews ask questions on start and stop dates of each AED taken, dose, frequency, changes in medication, and indication; demographic characteristics; cigarette smoking; alcohol intake; and use of illicit drugs; medical conditions; use of other medications; family history; and the results of any prenatal testing.

The study population was restricted to singleton, non-malformed liveborns whose mothers had complete follow-up data. A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance. Since the current study focused on neonatal outcomes, pregnant women enrolling after prenatal testing were not excluded from the analyses. Women were considered exposed if they used any AED during pregnancy. This group was divided into WWE (women with epilepsy) and WWOE (women without epilepsy), i.e., using the AEDs for indications such as migraine, anxiety/depression, or others. The infants of non-epileptic women not taking an AED (no-AED-WWOE) constituted our reference group. These were friends and relatives referred by AED- exposed participants since 2003. They received follow-up with the same methodology as the AED-exposed.

In the postnatal interview, the mother was asked about the infant's birth weight, length and head circumference, and any health problems. In addition, over 70% of the enrolled mothers provided medical records release forms. Medical records were received from the neurologist or

psychiatrist who prescribed the AED for 65% of all the mothers; and from the pediatrician for 59% of all the infants. In a validation study, there was a 99% agreement between the mother's verbal report and the doctors' records regarding major malformations.[18] The gestational age was calculated as the number of days from the last menstrual period (LMP), which was based on the woman's report and usually estimated by first trimester ultrasound. We determined the percentile for birthweight for each infant based on the gestational age, using US race-specific standards (stratification by sex gave the same results).[19] We defined small for gestational age (SGA) infants as those whose birthweight is below the 10th percentile given their gestational age at birth. Preterm delivery was defined as gestational age at birth <37 completed weeks. Secondary outcomes of interest were low birth weight (LBW, <2,500 g) and birth length. Subjects with missing values for birth weight, gestational age, or birth length were excluded from the respective analyses. Head circumference measurements were available for a small proportion of infants, a sample too small to produce any stable estimates.

Both the baseline covariates and the perinatal outcomes in each exposed group were compared with the un-exposed reference group. For categorical outcomes, we estimated crude and adjusted relative risks (RR) and their 95% confidence interval (CIs) using log-binomial multivariable logistic regression. Potential confounders considered included calendar year and maternal age, race, diabetes, cigarette smoking, alcohol use, periconceptional folic acid supplementation, illicit drug use, and education. All covariates were included in the model one at a time as categorical except for maternal age that was considered continuous. The a priori criteria was to include covariates in the model if they moved the RR estimate more than 10%.

We conducted the following sensitivity analyses: 1) We stratified the analyses by smoking and non-smoking during pregnancy to further explore the role of smoking as a confounder or effect modifier; 2) studied separately women exposed to monotherapy versus to more than one AED during pregnancy, including those who added or switched to different AEDs; 3) studied separately women with and women without seizures during pregnancy among women with epilepsy; 4) explored the risk of SGA for specific AEDs in monotherapy; 5) evaluated the effect of gestational timing of exposure; and 6) assessed dose effects.

All analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC). The study has been approved by the Human Studies Committee of the Massachusetts General Hospital and Partners HealthCare. Informed consent is obtained verbally at enrollment.

RESULTS

From February 1, 1997 through January 1, 2017, the number of enrolled women was 9,819 in the AED exposed and 704 in the unexposed control group (Figure 1). The corresponding number of eligible women was 7,473 and 522, respectively, after applying inclusion criteria and excluding 36 unexposed women with epilepsy. Among women on AEDs, 0.7% resulted in stillbirth or neonatal death and 2.7% had major malformations, compared to 0.2% and 1.3% in the unexposed group.[4] The number of spontaneous abortions and elective terminations was also higher among AED users.[20] The main indications for AED were epilepsy (91%), depression (5.3%), anxiety (1.1%), and migraine (1.1%). (Of note, the North American AED Pregnancy Registry targets women with epilepsy, therefore the distribution of indications for usage does not reflect that in the general population.)

Compared to the unexposed group, women on AEDs were more often single and less educated, and a higher proportion smoked cigarettes (*p values<0.01*). Within AED users, WWOE were less likely to use preconceptional folic acid (*p value<0.01*) and tended to have more insulin-dependent diabetes (*p values=0.06*). Table 1.

The mean birth weight for the reference group was 3,453 grams (Table 2). Compared to these unexposed pregnancies, prenatal exposure to AED was associated with a mean lesser birth weight of 110 grams among WWE and 136 grams among WWOE (*p values<0.01*). There was a left shift in the birth weight distribution among the offspring of women who used AEDs, both for WWE and WWOE. Although smoking had an additive weight lowering effect, the shift associated with AED exposure was observed both among smokers and among non-smokers. The mean infant's length at birth for unexposed women was 51.1 cm. Use of AED was associated with a mean lesser length of 0.5 centimeters both for WWE and WWOE (p values<0.01).

The mean gestational length was 39 weeks for the three groups. However, there was a higher proportion of preterm deliveries in women who used AEDs, for both WWE (9.3%) and WWOE (10.5%) compared to the reference group (6.2%) [Table 2]. After adjustment for measured confounders the RR was 1.5 (95%CI 1.0 to 2.1) and 1.5 (1.0 to 2.4) for WWE and WWOE, respectively. Delivery by Cesarean section was more common among women who used AEDs, for both WWE (33.7%) or WWOE (36.0%), than in the reference (28.8%). (Information on the specific indication for the Cesarean section was not available.) The higher proportion of preterm birth in women on AEDs remained among infants delivered vaginally; it was 7.9% for WWE, 9.6% for WWOE and 4.5% for the reference group (*p values<0.05*).

The prevalence of SGA was 5.0% for the unexposed reference group. Within users of AEDs, the prevalence was 10.9% for WWE and 11.0% for WWOE (Table 3). After adjustment for measured confounders the RR was 2.0 (95%CI 1.3 to 3.0) and 1.9 (1.2 to 2.9) for WWE and WWOE, respectively. Similar results were observed when restricting to non-smokers.

Among WWE on AEDs, having seizures and being on polytherapy were associated with worse pregnancy outcomes (Table e1). The prevalence of SGA among WWE on monotherapy without seizures during pregnancy was 9.5%, among WWE on monotherapy with seizures was 10.7%; among WWE on polytherapy without seizures during pregnancy was 13.4%; and among WWE on polytherapy with seizures was 14.3 % (Table 4). Compared to WWE on monotherapy and no seizures, the adjusted RR for WWE on polytherapy and with seizures was 1.4 (95%CI 1.1 to 1.7).

Given the similar results for WWE and WWOE, we combined these AED exposed groups for the analysis of specific drugs. The prevalence of SGA was different for different drugs, with topiramate, phenobarbital, and zonisamide monotherapies presenting the highest risks (Figure 2). Compared to lamotrigine monotherapy, the adjusted RR for topiramate, phenobarbital, and zonisamide monotherapies were 2.4 (95%CI 1.8 to 3.1), 2.4 (95%CI 1.6 to 3.6), and 1.9 (95%CI 1.2 to 3.0). (Of note, using lamotrigine as an active reference resulted in more balanced maternal characteristic across groups, although women prescribed topiramate still had lower education and were more frequently smokers than those on lamotrigine. We adjusted by these characteristics in the model.) The differences were not explained by lower maternal weight. In a subsample of women with data on weight (study years 2008 onward), the median maternal pre-pregnancy weight was actually higher for topiramate users (150 lbs) than for lamotrigine users (144 lbs).

Compared to lamotrigine, prenatal exposure to topiramate or zonisamide were associated with a mean lesser birth length of 1 centimeter (*p value <0.01*); the difference for phenobarbital was of 0.5 centimeters (*p value 0.05*).

The effects of specific gestational periods of exposure could not be assessed because most women used their AED throughout pregnancy. The exception was topiramate due to a larger proportion of women with intermittent use for migraine: The prevalence of SGA was 8.2% for women who stopped topiramate before the third trimester and 20.2% for those who continued its use later in pregnancy (*p value*=0.043). There was no apparent dose effect on the prevalence of SGA for lamotrigine, zonisamide or phenobarbital at the dose ranges used in our population. However, the prevalence of SGA was 8.5% for mean topiramate doses <50 mg and 19.9% for higher doses (*p value 0.04*).

DISCUSSION

In this prospective pregnancy cohort, women on AEDs during pregnancy had a higher risk of delivering infants with low birth weight for their gestational age. The association was present for women with epilepsy as well as for women with other neuropsychiatric indications. Findings also suggest an association between AED use and preterm birth. Within WWE on AEDs, seizures during pregnancy and polytherapy were associated with a higher frequency of both prematurity and SGA. The risk of SGA varied by AED: infants born to women on topiramate, zonisamide and phenobarbital were more often SGA and shorter in length.

Previous studies had reported that WWE are at increased risk for preterm labor and poor fetal growth,[1,13-15,21-24] particularly when treated with AEDs.[25] Although others did not find these

associations.[16,26-29] Maternal seizures[30] and polytherapy[13,15,31] have also been associated with poor fetal growth. Whether the associations are caused by factors associated with the condition or by the treatments has been a source of controversy. Most AEDs are thought to be weight neutral or stimulate weight gain in the patient taking them;[7] except for topiramate and zonisamide, which are thought to cause weight loss,[8-10] and have been marketed as weight-loss treatments. Long-term treatment of infants for up to one year has been shown to reduce length, weight, and head circumference.[32] At least four epidemiological studies have reported lower birth weight for infants exposed to topiramate in utero.[11-14] The different distribution of individual AEDs in different populations might explain the apparent discrepancies among studies.

Being born SGA has been associated with worse health outcomes not only in the perinatal period, but also later in life.[33-37] However, the long term consequences of the potential AED - related SGA are unknown. The prognosis likely depends on the ultimate cause or mechanism of poor growth. There is no information on whether SGA related to AED in utero exposure (or the indications) is associated with long term complications. Our data are currently insufficient to determine whether the apparent growth restriction is symmetric or asymmetric (brain sparing). There are little data to assess any association between topiramate or zonisamide exposure and neonatal mortality, developmental shortcomings, behavioral aberrations, or poor performance in school.[38]

The association found in this and other studies between AEDs and perinatal outcomes may be causal, or due to unbalanced risk factors among comparison groups. As we argue below, our results cannot be explained by differences in the distribution of smoking or pre-pregnancy

maternal weight, and are unlikely to be explained by the underlying indication for these drugs: Since smokers have smaller infants[36,39] and the proportion of smokers was larger in AED users in our population than in the reference group, our findings could have been explained by unbalanced maternal smoking in the two groups. However, the association between AEDs and SGA remained within non-smokers and further shifted the birth weight curve towards lower values within. Thus, findings strongly suggest that there is an independent and additive effect of smoking and AEDs.

Maternal weight is also known to correlate with fetal growth.[36,39] We were not able to adjust for it because maternal weigh has been systematically collected by the registry only in recent study years. In the subsample of participants with data available, topiramate users had higher pre-pregnancy weights than non-users or users of other AEDs. This is consistent with population-based data from the US where young women on AEDs had a similar body mass index than non-users; except for topiramate users, that were more frequently overweight.[40] Thus, adjustment for maternal weight would have resulted in similar or larger relative risk estimates for topiramate. Regarding other potential confounders, since adjustment for education and other sociodemographic characteristics had very little impact on the relative risk estimates, substantial confounding by these risk factors seems unlikely.

Regarding confounding by indication, we found the association with adverse prenatal outcomes for both WWE and for WWOE. Although this finding may suggest that the treatments are responsible for the association, there could be a predisposition of having SGA infants for women with epilepsy and for women with the other indications. Women with non-epilepsy indications for AEDs (e.g., depression, bipolar disorders) have also been shown to be at a higher risk for

preterm and SGA infants.[14,41-50] On the other hand, comparisons among different AEDs minimize this potential confounding by indication suggest that different drugs may be associated with different risk. Yet, there could be residual confounding, if different types of epilepsy treated preferentially with specific AEDs were associated with fetal growth. Moreover, the higher risk among women on polytherapy could reflect a dose effect; although it may also reflect a type of epilepsy more difficult to control. Of note, use of polytherapy was associated with having seizures during pregnancy.

The North American AED Pregnancy Registry relies on volunteers, who may be better functioning, with less severe epilepsy, and might have lower risk of SGA infants than the general population of women with epilepsy. In fact, the unexposed reference group had a lower prevalence of SGA than that expected by definition in the general population (i.e. 10%). We can only assume that the relative risks for WWE and WWOE observed in our study would be similar in the general population. It is plausible that in populations with higher baseline risks of adverse neonatal outcomes, the relative effect of AEDs on fetal growth may be more modest. In addition, we did not have information on blood levels; factors that affect AEDs levels (e.g., compliance, drug interactions) may also affect the strength of the association between the dose prescribed and the outcomes.

From a clinical point of view, the most relevant question is which specific AED to use for women of childbearing age, and for pregnant women. Patients and health care providers need to consider the efficacy for each individual patient and the safety for the mother and the developing infant. Comparisons among different AEDs is warranted since most WWE require pharmaceutical treatment. Additionally, clinicians caring for the pregnancies of women on AED

should be aware of the heightened potential for decreased fetal growth and consider modifying prenatal surveillance accordingly. While the question of whether it is the drugs or the indication remains, we do have enough information to know that WWE and WWOE on AEDs are high risk pregnancies and both the mother and the infant deserve special clinical attention.

In conclusion, we found an increased risk of being SGA at birth and an increased risk of premature birth among newborns exposed to AEDs *in utero*, compared to infants in the unexposed reference group, for both WWE and women with other neuropsychiatric disorders. The risk is higher in women on polytherapy and in women with seizures during pregnancy; and it is highest for topiramate, phenobarbital and zonisamide.

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Author Contributions:

Authors Contributions: LBH, MY and AH were responsible for the conception and design of the study; SHD was responsible for the analysis of the data, drafting of the text and preparing the figures; TFM and PBP contributed to the interpretation of results; all authors contributed to drafting or revising of the manuscript and has approved the manuscript as submitted the text.

Potential Conflicts of Interest:

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REFERENCES

1. Harden CL, Pennell PB, Koppel BS, et al. Management issues for women with epilepsy--focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009;50:1247-55.
2. Adedinsewo DA, Thurman DJ, Luo YH, Williamson RS, Odewole OA, Oakley GP, Jr. Valproate prescriptions for nonepilepsy disorders in reproductive-age women. Birth defects research Part A, Clinical and molecular teratology 2013;97:403-8.
3. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. American journal of obstetrics and gynecology 2011;205:51 e1-8.
4. Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology 2012;78:1692-9.
5. 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. The Lancet Neurology 2013;12:244-52.
6. Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA : the journal of the American Medical Association 2013;309:1696-703.
7. Sheth RD, Montouris G. Metabolic effects of AEDs: impact on body weight, lipids and glucose metabolism. International review of neurobiology 2008;83:329-46.

8. Gadde KM, Franciscy DM, Wagner HR, 2nd, Krishnan KR. Zonisamide for weight loss in obese adults: a randomized controlled trial. JAMA : the journal of the American Medical Association 2003;289:1820-5.
9. McElroy SL, Kotwal R, Hudson JI, Nelson EB, Keck PE. Zonisamide in the treatment of binge-eating disorder: an open-label, prospective trial. The Journal of clinical psychiatry 2004;65:50-6.
10. Gadde KM, Kopping MF, Wagner HR, Yonish GM, Allison DB, Bray GA. Zonisamide for Weight Reduction in Obese Adults: A 1-Year Randomized Controlled Trial. Archives of internal medicine 2012:1-8.
11. Ornoy A, Zvi N, Arnon J, Wajnberg R, Shechtman S, Diav-Citrin O. The outcome of pregnancy following topiramate treatment: a study on 52 pregnancies. Reprod Toxicol 2008;25:388-9.
12. Hernandez-Diaz S, Mittendorf R, Smith CR, Hauser WA, Yerby M, Holmes LB. Association between topiramate and zonisamide use during pregnancy and low birth weight. Obstetrics and gynecology 2014;123:21-8.
13. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. Journal of neurology 2014;261:579-88.
14. Kilic D, Pedersen H, Kjaersgaard MI, et al. Birth outcomes after prenatal exposure to antiepileptic drugs--a population-based study. Epilepsia 2014;55:1714-21.
15. Artama M, Gissler M, Malm H, Ritvanen A. Effects of maternal epilepsy and antiepileptic drug use during pregnancy on perinatal health in offspring: nationwide, retrospective cohort

study in Finland. Drug safety : an international journal of medical toxicology and drug experience 2013;36:359-69.

16. McPherson J, Harper L, Odibo A, Roehl K, Cahill A. Maternal seizure disorder and risk of adverse pregnancy outcomes. American journal of obstetrics and gynecology 2013;208:e1-5.
17. Holmes L, Wyszynski D, Lieberman E. The Antiepileptic Drug Pregnancy Registry: a six year experience. Archives of neurology 2004;61:673-8.
18. Holmes LB, Baldwin E, Habecker E, Glassman L, Wong S, Wyszynsky DF. Increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy. Neurology 2008;70:2152-58.
19. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC pediatrics 2003;3:6.
20. Margulis AV, Mittleman MA, Glynn RJ, Holmes LB, Hernandez-Diaz S. Effects of gestational age at enrollment in pregnancy exposure registries. Pharmacoepidemiology and drug safety 2015;24:343-52.
21. MacDonald SC, Bateman BT, McElrath TF, Hernandez-Diaz S. Mortality and Morbidity During Delivery Hospitalization Among Pregnant Women With Epilepsy in the United States. JAMA neurology 2015.
22. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. Epilepsia 2009;50:2130-9.
23. Fairgrieve SD, Jackson M, Jonas P, et al. Population based, prospective study of the care of women with epilepsy in pregnancy. BMJ 2000;321:674-5.

24. Hvas CL, Henriksen TB, Ostergaard JR. Birth weight in offspring of women with epilepsy. Epidemiologic reviews 2000;22:275-82.
25. Pennell PB, Klein AM, Browning N, et al. Differential effects of antiepileptic drugs on neonatal outcomes. Epilepsy & behavior : E&B 2012;24:449-56.
26. Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: an obstetric perspective. American journal of obstetrics and gynecology 2004;190:371-9.
27. Mawer G, Briggs M, Baker GA, et al. Pregnancy with epilepsy: obstetric and neonatal outcome of a controlled study. Seizure : the journal of the British Epilepsy Association 2010;19:112-9.
28. Saleh AM, Abotalib ZM, Al-Ibrahim AA, Al-Sultan SM. Comparison of maternal and fetal outcomes, in epileptic and non-epileptic women. Saudi medical journal 2008;29:261-6.
29. Viinikainen K, Heinonen S, Eriksson K, Kalviainen R. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. Epilepsia 2006;47:186-92.
30. Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. Archives of neurology 2009;66:979-84.
31. Harden CL, Meador KJ, Pennell PB, et al. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009;50:1237-46.

32. Antel J, Hebebrand J. Weight-reducing side effects of the antiepileptic agents topiramate and zonisamide. In: Joost HG, ed. Appetite Control, Handbook of Experimental Pharmacology. Verlag Berlin Heidelberg: Springer; 2012:433-66.
33. Halbreich U. The association between pregnancy processes, preterm delivery, low birth weight, and postpartum depressions--the need for interdisciplinary integration. American journal of obstetrics and gynecology 2005;193:1312-22.
34. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. The New England journal of medicine 1999;340:1234-8.
35. Luyckx V, Bertram J, Brenner B. Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. Lancet 2013;382:273-84.
36. La Merrill M, Stein CR, Landrigan P, Engel SM, Savitz DA. Prepregnancy body mass index, smoking during pregnancy, and infant birth weight. Annals of epidemiology 2011;21:413-20.
37. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. Endocrine reviews 2007;28:219-51.
38. Bromley RL, Calderbank R, Cheyne CP, et al. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. Neurology 2016;87:1943-53.
39. Goetzinger KR, Cahill AG, Macones GA, Odibo AO. The relationship between maternal body mass index and tobacco use on small-for-gestational-age infants. American journal of perinatology 2012;29:153-8.
40. Dugan K, Margulis A, Hernandez-Diaz S. Topiramate for weight loss Pharmacoepidemiology and drug safety 2011;20:S1-S382.

41. Dayan J, Creveuil C, Herlicoviez M, et al. Role of anxiety and depression in the onset of spontaneous preterm labor. Am J Epidemiol 2002;155:293-301.
42. Dayan J, Creveuil C, Marks MN, et al. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. Psychosomatic medicine 2006;68:938-46.
43. Preti A, Cardascia L, Zen T, et al. Obstetric complications in patients with depression--a population-based case-control study. Journal of affective disorders 2000;61:101-6.
44. Sandman CA, Wadhwa PD, Chicz-DeMet A, Dunkel-Schetter C, Porto M. Maternal stress, HPA activity, and fetal/infant outcome. Annals of the New York Academy of Sciences 1997;814:266-75.
45. Weinstock M. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Progress in neurobiology 2001;65:427-51.
46. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Heinen AG, van Geijn HP. Psychosocial predictors of low birthweight: a prospective study. British journal of obstetrics and gynaecology 1999;106:834-41.
47. McAnarney ER, Stevens-Simon C. Maternal psychological stress/depression and low birth weight. Is there a relationship? Am J Dis Child 1990;144:789-92.
48. Steer RA, Scholl TO, Hediger ML, Fischer RL. Self-reported depression and negative pregnancy outcomes. Journal of clinical epidemiology 1992;45:1093-9.
49. Hoffman S, Hatch MC. Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women. Health psychology : official journal of the Division of Health Psychology, American Psychological Association 2000;19:535-43.

50. Field T, Diego M, Hernandez-Reif M, et al. Prenatal anger effects on the fetus and neonate. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2002;22:260-6.

Figure Legends

Figure 1. Enrollment and eligibility of participants. North American AED Registry 1997-2016.

Figure 2. Prevalence of SGA (bars) at birth and adjusted relative risk (dots) and 95% confidence interval (error bars) in infants born to women on specific AEDs in monotherapy at any time during pregnancy compared to those on lamotrigine (reference). Number of exposed provided at the base of each bar.

Table 1. Characteristics of the women with and without epilepsy and either unexposed or exposed to AEDs during pregnancy.

Categories*	No AED & WWOE	AED & WWE	AED & WWOE
	n=486	n=6777	n=696
Age (mean, SD)	31.5 (4.2)	29.7 (5.3)	31.3 (5.4)
Education **			
< Grade 12	17 (3.5)	871 (16.6)	98 (15.7)
Junior Graduate (2-year)	58 (12.0)	1202 (22.9)	165 (26.4)
College Graduate (4-year)	198 (40.9)	1988 (37.9)	215 (34.5)
Post College	211 (43.6)	1186 (22.6)	146 (23.4)
Married **	461 (95.3)	4292 (81.9)	454 (72.9)
Caucasian	433 (89.3)	5807 (85.7)	632 (90.9)
Primiparity	173 (35.6)	2758 (40.7)	246 (35.3)
Folic Acid Supplement at LMP **	333 (68.5)	4767 (70.3)	360 (51.7)
Cigarette Smoking **			
None	458 (94.4)	5925 (87.6)	524 (75.4)
>None, <1/2 pack	15 (3.1)	325 (4.8)	59 (8.5)
>1/2 pack, <1 pack	6 (1.2)	205 (3.0)	46 (6.6)
>1 pack	3 (0.6)	258 (3.8)	53 (7.6)
Yes, but unknown	3 (0.6)	54 (0.8)	13 (1.9)
Alcohol			
None	342 (70.7)	5126 (75.8)	493 (70.9)
Moderate (1-5 drinks/week)	116 (24.0)	1412 (20.9)	167 (24.0)
>5 drinks/week	17 (3.5)	118 (1.8)	22 (3.2)
Yes, but unknown	9 (1.9)	104 (1.5)	13 (1.9)
Diabetes **	7 (2.1)	100 (2.1)	21 (4.5)
Age First Seizure (mean, SD)	NA	16.6 (8.6)	NA
Seizures During Pregnancy	NA	2247 (33.2)	NA

* Columns present numbers and proportions (in parenthesis) unless otherwise specified. Numbers might not add to the total due to missing values.

** All unadjusted p-values<0.01, except for diabetes (p-value 0.06).

Table 2. Risk of small for gestational age (SGA), low birth weight (LBW) and preterm delivery among singleton liveborn infants.

Outcomes	No AED & WWOE n=486	AED & WWE n=6777	AED & WWOE n=696
Child's Birthweight, gr (mean, SD)	3453 (537.4)	3343 (561.5)	3317 (544.7)
Gestational age, weeks (mean, SD)	39.2 (1.9)	39.1 (1.9)	39.0 (1.9)
Child's Length, cm (mean, SD)	51.1 (3.4)	50.6 (3.3)	50.6 (3.2)
LBW, N(%)	22 (4.6)	419 (6.4)	42 (6.4)
Preterm, N(%)	30 (6.2)	613 (9.3)	69 (10.5)
SGA, N(%)	24 (5.0)	713 (10.9)	72 (11.0)

Table 3. Relative risk (RR) and 95% confidence interval (CI) of small for gestational age (SGA) and preterm delivery among singleton liveborn infants exposed to AEDs in mono or polytherapy compared with unexposed infants.

Outcomes	No AED & WWOE n=486	AED & WWE n=6777	AED & WWOE n=696
SGA			
N (%)	24 (5.0)	713 (10.9)	72 (11.0)
Crude RR (95%CI)	Reference	2.2 (1.5-3.2)	2.2 (1.4-3.4)
Adjusted RR (95%CI)	Reference	2.0 (1.3-3.0)	1.9 (1.2-2.9)
Preterm			
N (%)	30 (6.2)	613 (9.3)	69 (10.5)
Crude RR (95%CI)	Reference	1.5 (1.1-2.1)	1.7 (1.1-2.5)
Adjusted RR (95%CI)	Reference	1.5 (1.0-2.1)	1.5 (1.0-2.4)

Adjusted for maternal age, parity, smoking, and education.

Table 4. Relative risk (RR) and 95% confidence interval (CI) of small for gestational age (SGA) associated with seizures during pregnancy and mono/poly-therapy among WWE on AEDs.

Therapy	Seizures	N	SGA		Adjusted RR	
			N (%)		95% CI	
Monotherapy	No seizures	3647	347	(9.5)	Reference	
Monotherapy	Seizures	1373	147	(10.7)	1.1	(0.9-1.3)
Polytherapy	No seizures	700	96	(13.7)	1.3	(1.1-1.7)
Polytherapy	Seizures	839	122	(14.5)	1.4	(1.1-1.7)

Adjusted for maternal age, parity, smoking, and education.

Table e1. Risk of small for gestational age (SGA), low birth weight (LBW) and preterm delivery among WWE on AEDs, stratified by seizures during pregnancy or mono/poly-therapy.

Outcomes	No seizures		Seizures			Monotherapy		Polytherapy		
	n=4347		n=2213		*p value*	n=5020		n=1539		*p value*
LBW N(%)	248	(5.7)	171	(7.7)	0.002	281	(5.6)	137	(8.9)	<0.001
Preterm, N(%)	367	(8.4)	246	(11.1)	0.001	411	(8.2)	201	(13.1)	<0.001
SGA, N(%)	443	(10.2)	270	(12.2)	0.015	494	(9.8)	218	(14.2)	<0.001

Figure 1. Enrollment and eligibility of participants. North American AED Registry 1997-2016.

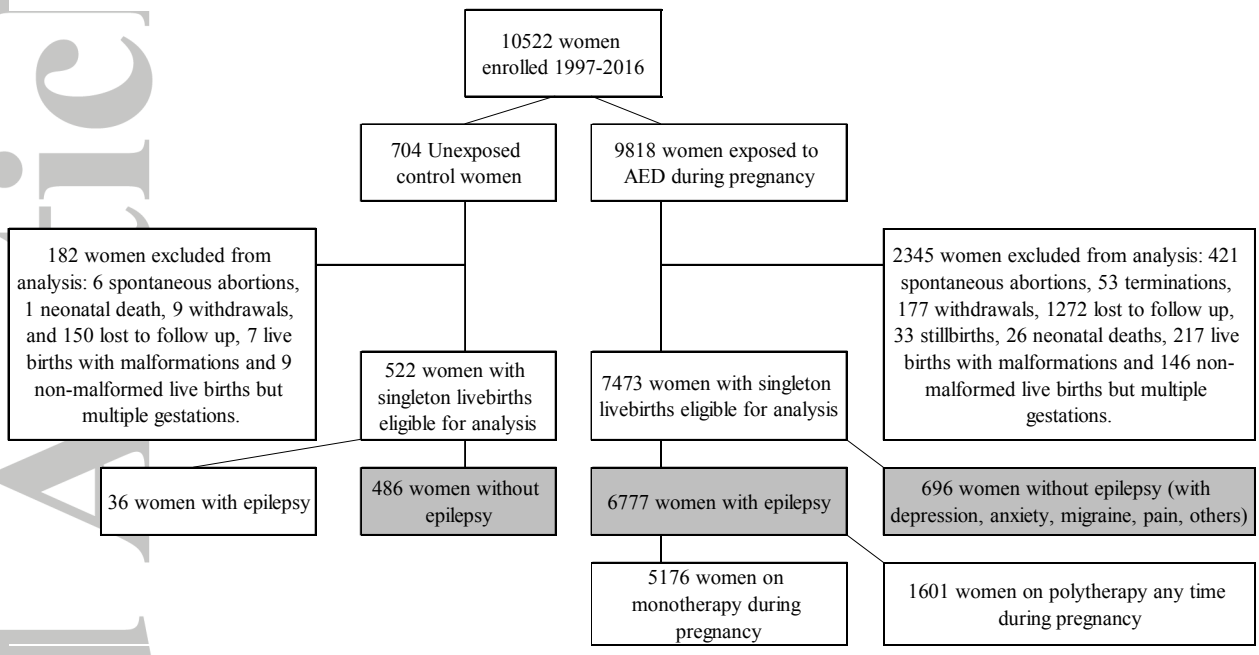
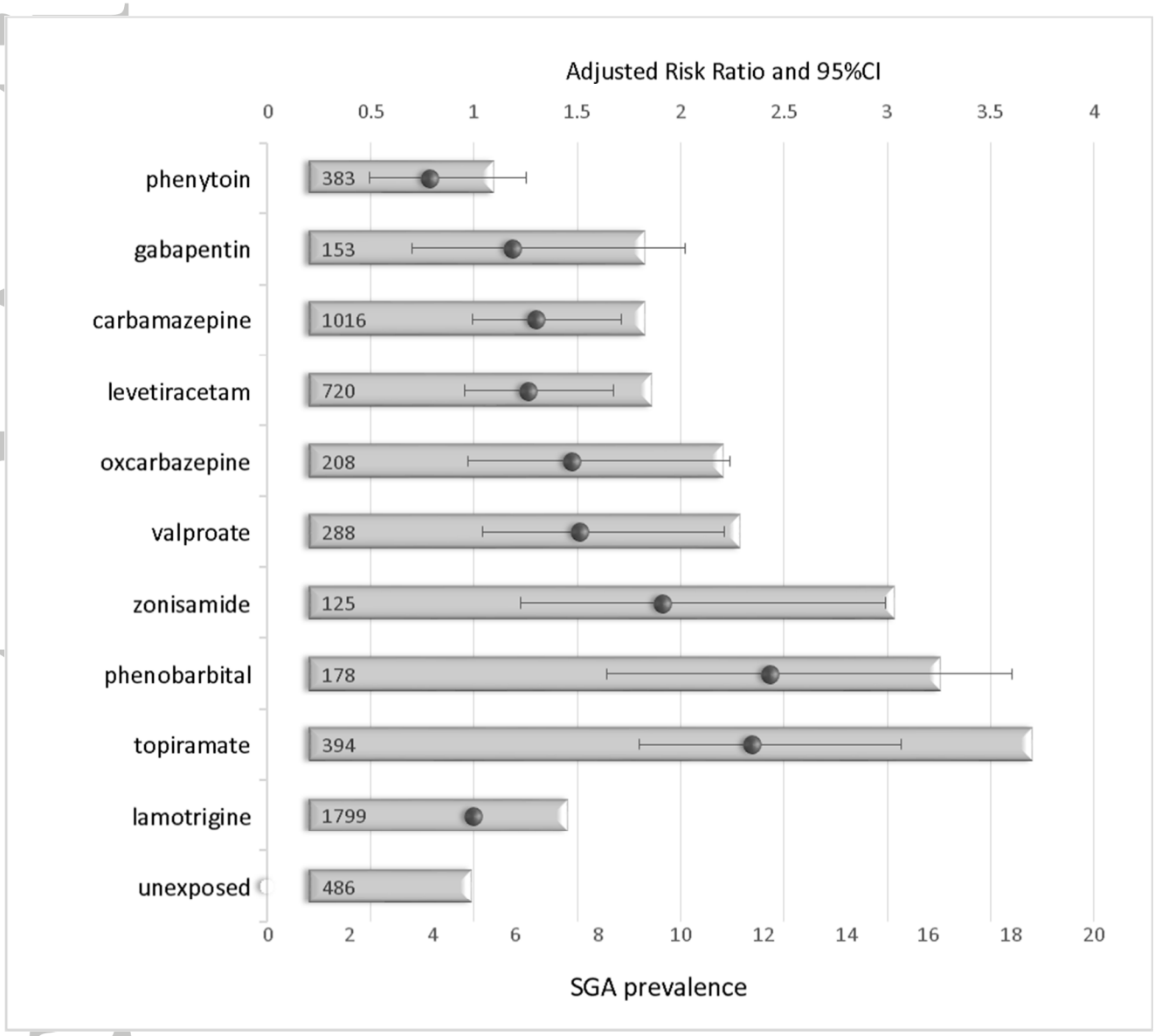
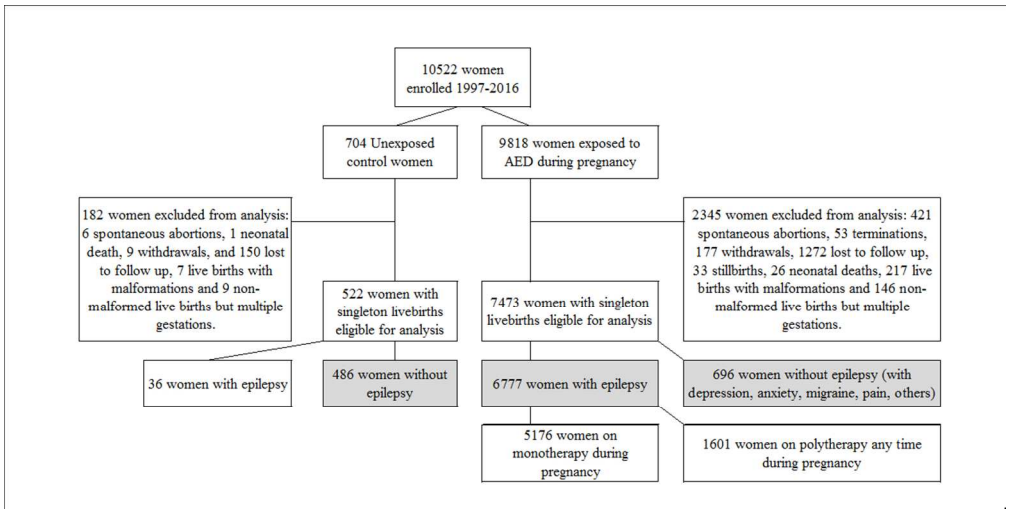


Figure 2. Prevalence of SGA (bars) at birth and adjusted relative risk (dots) and 95% confidence interval (error bars) in infants born to women on specific AEDs in monotherapy at any time during pregnancy compared to those on lamotrigine (reference). Number of exposed provided at the base of each bar.





Enrollment and eligibility of participants. North American AED Registry 1997-2016.

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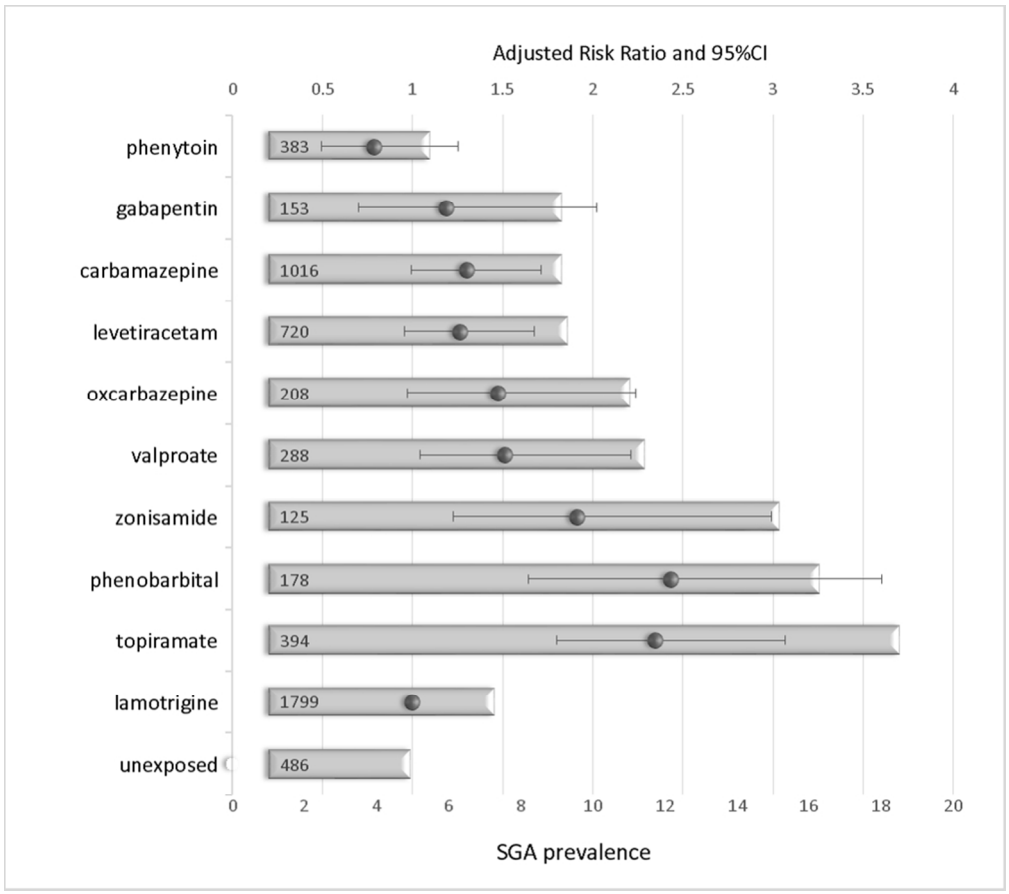

Prevalence of SGA (bars) at birth and adjusted relative risk (dots) and 95% confidence interval (error bars) in infants born to women on specific AEDs in monotherapy at any time during pregnancy compared to those on lamotrigine (reference). Number of exposed provided at the base of each bar.

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