Original Research

Association Between Topiramate and Zonisamide Use During Pregnancy and Low Birth Weight

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OBJECTIVE: To assess the possible effects of topiramate and zonisamide use during pregnancy on fetal growth.

METHODS: The study population was the singleton liveborns born to women who enrolled in the North American Antiepileptic Drug Pregnancy Registry between 1997 and 2012. Data were collected through telephone interviews at enrollment, 7 months of gestation, and postpartum. The prevalence of small for gestational age at birth among neonates exposed to topiramate and to zonisamide when either was used as monotherapy during pregnancy was compared with that among neonates exposed to lamotrigine monotherapy, a weight-neutral therapy, and the most common antiepileptic drug in the Registry. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated with multivariable log-binomial regression to control for potential confounders.

RESULTS: Data were available for 347 topiramate, 98 zonisamide, and 1,581 lamotrigine-exposed neonates. The mean gestational length was 39 weeks for all comparison groups. Prenatal exposure to topiramate or zonisamide was associated with a mean lower birth weight of 221 and 202 g, respectively, and a mean lesser neonatal length of 1 cm as compared with lamotrigine exposure ($p<.01$). The prevalence of small for gestational age was 6.8% for lamotrigine, 17.9% for topiramate (RR 2.4, 95% CI 1.8–3.3) and 12.2% for zonisamide (RR 1.6, 0.9–2.8). Similar results were found when a group of 457 unexposed neonates was used as the reference.

CONCLUSIONS: Topiramate and zonisamide have been shown to reduce weight in adults. Our finding of a decrease in mean birth weight and length among neonates exposed in utero raises concern.

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LEVEL OF EVIDENCE: II

Topiramate is approved in the United States for the treatment of seizures and migraine. However, it has been frequently used for other off-label indications, including weight loss. The significant reduction of body weight observed in patients treated for epilepsy as well as a secondary end point in epilepsy studies prompted a series of clinical trials, which confirmed its efficacy in weight loss.[1–4] Recently, a topiramate-containing weight loss product (phentermine/topiramate) has been approved by the U.S. Food and Drug

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Administration[5–7] despite some concerns regarding the risk of oral clefts in neonates exposed in utero.[7–10]

Most antiepileptic drugs are weight-neutral or stimulate weight gain.[11] Other than topiramate, only zonisamide had been shown to cause major weight loss.[12–15] There has been limited information on the potential weight loss side effects of topiramate or zonisamide in pregnant women and their neonates. In premarketing studies, long-term treatment of infants for up to 1 year showed reductions in length, weight, and head circumference.[16] Postmarketing, Ornoy et al[17] reported decreased birth weight in 41 topiramate in utero-exposed neonates.

We present the findings in the North American Antiepileptic Drug Pregnancy Registry. The objective was to estimate the risk of uterine growth restriction in neonates whose mothers had taken topiramate or zonisamide as monotherapy during pregnancy and to assess whether this risk was increased relative to neonates born to women exposed to lamotrigine, a purportedly weight-neutral antiepileptic drug[11,12] commonly used in our population, as well as relative to women who had not taken an antiepileptic drug, ie, an unexposed comparison group.

PATIENTS AND METHODS

The North American Antiepileptic Drug Pregnancy Registry is an ongoing surveillance system of pregnant women who are taking an antiepileptic drug for any reason.[18–20] Women self-enroll by calling a toll-free telephone number. To be eligible, a woman must be pregnant and to have taken antiepileptic drugs at some point during her pregnancy.

Women were interviewed at 1) enrollment; 2) 7 months of gestation; and 3) 8–12 weeks after the expected date of delivery. The computer-assisted interviews included questions on start and stop dates of each antiepileptic drug taken, dose, frequency, changes in medication, indication, and, if epileptic, number and type of seizures during pregnancy; demographic characteristics; habits such as 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 cohort was restricted to women who had singleton, nonmalformed liveborns and who had complete follow-up data. A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance. The proportion of women excluded for malformations was 2% for lamotrigine, 4% for topiramate, and 0% for zonisamide. Women were considered exposed if they used topiramate or zonisamide, as monotherapy, during pregnancy. Our primary reference group was women exposed to lamotrigine monotherapy, because it has been the most commonly reported antiepileptic drug in the Registry and is considered weight-neutral.[12] This active reference group minimizes confounding by indication, because most participants in the groups compared (ie, topiramate and zonisamide compared with lamotrigine) will have epilepsy. A secondary internal reference group was pregnant, nonepileptic women not taking an antiepileptic drug who had been recruited since 2003. These were friends and relatives referred by antiepileptic drug-exposed participants. They received follow-up with the same methodology as those exposed. The neonates of these mothers constituted the unexposed comparison group for exposed neonates.

In the postnatal interview, the mother was asked about the birth status of the neonate, including neonatal weight, length and head circumference, and any health problems. In addition, she was asked to sign and return a medical record release form. The neonates' doctors were asked to return copies of their examination findings through the first 12 weeks of life. More than 70% of the enrolled mothers provided medical records release forms. Medical records were received from the neurologist or psychiatrist who prescribed the antiepileptic drug 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 for the infants whose mothers had provided permission.[20] The gestational age was calculated using the number of days from the last menstrual period, which was based on the woman's report and typically estimated by first-trimester ultrasonography. We determined the percentile for birth weight for each neonate based on the gestational age using U.S. sex-specific standards.[21] We defined small-for-gestational-age (SGA) neonates as those below the 10th percentile corrected for their gestational age stratified by sex (stratification by race gave the same results). Secondary outcomes of interest were low birth weight (less than 2,500 g) and preterm delivery (gestational age at birth less than 37 completed weeks), birth length, and head circumference. Participants with missing values for birth weight (n=9), gestational age (n=1), birth length (n=94), or head circumference (n=1,775) were excluded from the respective analyses.

We compared the sociodemographic and clinical characteristics of women exposed to the specific drugs. The growth parameters in each exposed group were compared with the lamotrigine-exposed reference group. For categorical outcomes, we estimated

both crude and adjusted relative risks (RRs) and their 95% confidence intervals (CIs) using log-binomial logistic regression. Potential confounders included maternal age, race, education, alcohol use, cigarette smoking, periconceptional folic acid supplementation, illicit drug use, chronic diseases (eg, type 1 diabetes mellitus), indication for use of antiepileptic drugs (epilepsy, migraine, or other), and calendar year. We retained in the models factors known to be associated with the outcome, although none of the potential confounder moved the RR estimate more than 10%.

We conducted the following sensitivity analyses: 1) we restricted the comparisons to women with epilepsy to assess the role of indication; 2) stratified the analyses by smoking and nonsmoking during pregnancy to assess the role of smoking; 3) evaluated use during the third trimester and use only before the third trimester to assess the effect of gestational timing of exposure; 4) evaluated the mean dose during pregnancy to assess dose effects; and 5) studied women exposed to more than one antiepileptic drug during pregnancy, including those who added or switched to different antiepileptic drugs to assess the effect of polytherapy.

All analyses were performed using SAS 9.2.

Our 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 September 1, 2012, the number of enrolled women eligible for analysis was 347 for topiramate, 98 for zonisamide, and 1,581 for lamotrigine monotherapies and 457 for the unexposed secondary control group (Fig. 1).

Compared with lamotrigine monotherapy users, women on topiramate or zonisamide monotherapy were more often single and less educated, a higher proportion smoked, and fewer had used preconceptional folic acid (Table 1). Most women used their antiepileptic drug for epilepsy, although 13.8% of topiramate users took their drug for migraine and 12.3% of lamotrigine users took their drug for mood disorders. (Of note, the North American Antiepileptic Drug Pregnancy Registry does not reflect the indications for use in the general population, because it targets women with epilepsy.) The sociodemographic and behavioral characteristics were more heterogeneous between antiepileptic drug users and the unexposed women who comprise the secondary comparison group.

The mean birth weight for lamotrigine was 3,402 g (median 3,402 g); for topiramate 3,181 g (3,232 g); for zonisamide 3,200 g (3,204 g); and for the unexposed

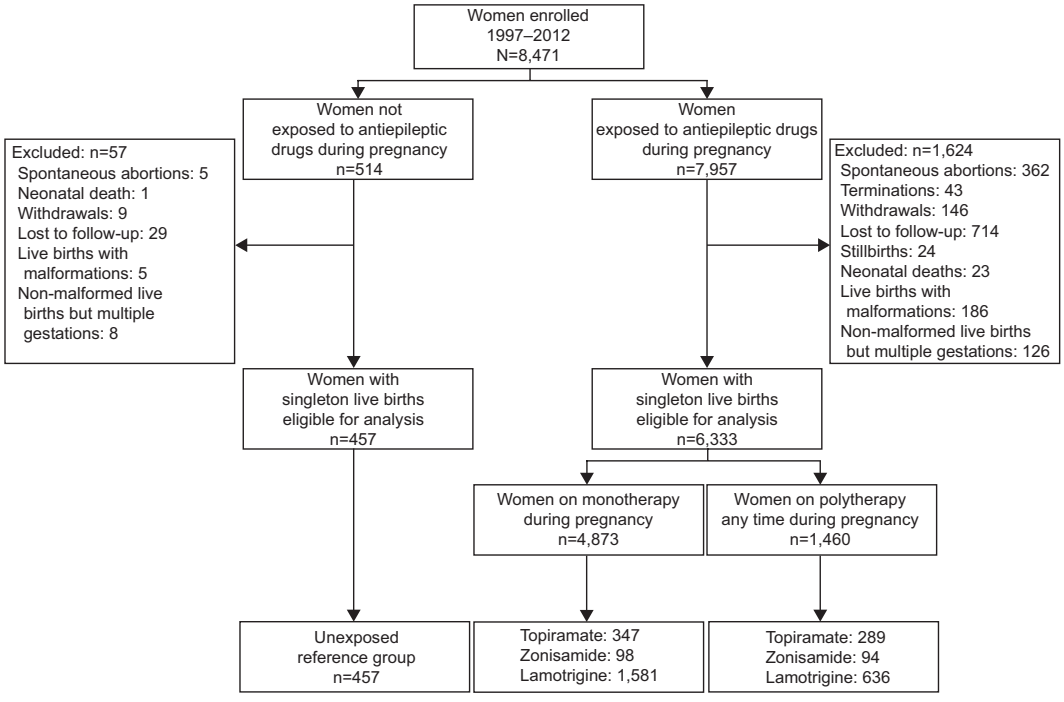

Fig. 1. Enrollment and eligibility of participants.

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Table 1. Characteristics of the Study Participants Either Unexposed or Exposed to Specific Antiepileptic Drugs in Monotherapy During Pregnancy

Categories*	Unexposed (n=457)†	Lamotrigine (n=1,581)	Topiramate (n=347)	Zonisamide (n=98)
Maternal age (y)	31±4.2	30±5.0	29±5.4	28±5.4
Mother's education				
Less than grade 12	17 (3.7)	190 (12.9)	92 (27.7)	20 (20.4)
Junior graduate (2 y)	57 (12.5)	288 (19.5)	91 (27.4)	21 (21.4)
College graduate (4 y)	185 (40.7)	591 (40.0)	103 (31.0)	38 (38.8)
Postcollege	196 (43.1)	407 (27.6)	46 (13.9)	19 (19.4)
Married	433 (95.2)	1,311 (88.9)	248 (74.7)	73 (74.5)
Mother Caucasian	412 (90.4)	1,396 (88.3)	312 (89.9)	83 (84.7)
Father Caucasian	406 (89.0)	1,337 (84.7)	288 (83.0)	74 (75.5)
Primiparity	159 (34.8)	668 (42.3)	146 (42.1)	57 (58.2)
Folic acid supplement at last menstrual period	317 (69.4)	1,241 (78.5)	208 (59.9)	68 (69.4)
Cigarette smoking				
None	429 (94.1)	1,438 (91.1)	289 (83.3)	87 (89.7)
More than none, less than half a pack/d	16 (3.5)	52 (3.9)	19 (5.5)	4 (4.1)
More than half a pack/d, less than 1 pack/d	6 (1.3)	38 (2.4)	18 (5.2)	4 (4.1)
More than 1 pack/d	3 (0.7)	33 (2.1)	16 (4.6)	2 (2.1)
Yes, but unknown	2 (0.4)	7 (0.4)	5 (1.4)	0 (0.0)
Alcohol				
None	319 (70.1)	1,219 (77.4)	274 (79.2)	83 (84.7)
Moderate (1–5 drinks/wk)	108 (23.7)	312 (19.8)	61 (17.6)	13 (13.3)
More than 5 drinks/wk	19 (4.2)	22 (1.4)	6 (1.7)	1 (1.0)
Yes, but unknown	9 (2.0)	23 (1.5)	5 (1.5)	1 (1.0)
Diabetes	5 (1.6)	17 (1.5)	4 (1.5)	0 (0.0)
Indication epilepsy	NA	1,373 (86.8)	283 (81.6)	97 (99.0)
Age first seizure (y)‡	NA	17.9±8.5	17.2±8.4	13.8±8.1
Seizures during pregnancy‡	NA	400 (29.1)	91 (32.2)	19 (19.6)

NA, not applicable.
Data are mean±standard deviation or n (proportion).
* Numbers might not add to the total owing to missing values.
† The unexposed internal comparison group was pregnant women not taking antiepileptic drugs who were recruited from among the friends and family members of the enrolled women taking an antiepileptic drug.
‡ Among patients with epilepsy.

groups 3,458 g (3,459 g) (Fig. 2). Compared with lamotrigine, prenatal exposure to topiramate and zonisamide were associated with a mean lesser birth weight of 221 g ($P<.001$) and 202 g ($P<.01$), respectively, and a mean lesser birth length of 1 cm ($P<.01$), whereas the mean gestational length was 39 weeks for the three antiepileptic drug groups (Table 2). Head circumference measurements were available on only 43 topiramate-exposed neonates and five zonisamide-exposed neonates, a sample too small to determine whether there were significant differences. There was a left shift in the birth weight distribution among the offspring of women who used topiramate compared with lamotrigine both among smokers and among nonsmokers (Fig. 3). Neonates born to topiramate users who smoked during pregnancy had the lowest mean birth weight (3,080 g).

The prevalence of SGA was 6.8% for lamotrigine; 17.9% for topiramate (adjusted RR compare to lamotrigine 2.4, 95% CI 1.8–3.3); and 12.2% for zonisamide (RR 1.6, 95% CI 0.90–2.8) -exposed neonates (Table 3). Maternal smoking was associated with a higher prevalence of neonatal SGA, whereas neither maternal antiepileptic drug indication nor having seizures during pregnancy was associated with SGA. Restriction to nonsmokers moved the adjusted SGA RRs to 2.6 (95% CI 1.8–3.6) for topiramate and to 2.0 (95% CI 1.2–3.6) for zonisamide. Restriction to women with epilepsy as the indication moved the adjusted RRs to 2.8 (95% CI 2.0–3.9) for topiramate and to 1.7 (95% CI 1.0–3.0) for zonisamide. Compared with the unexposed reference group, the RR was 3.5 (95% CI 2.1–5.7) for topiramate and 2.2 (1.1–4.4) for zonisamide.

Most women used their antiepileptic drug throughout pregnancy and the potential effects of specific gestational periods of exposure could not be assessed: only 11.8% of topiramate users (largely the migraine users), 3.1% of zonisamide users, and 2.4% of lamotrigine users had discontinued their antiepileptic drug by the third trimester. For topiramate, the prevalence of SGA was 7.3% for women who stopped before the

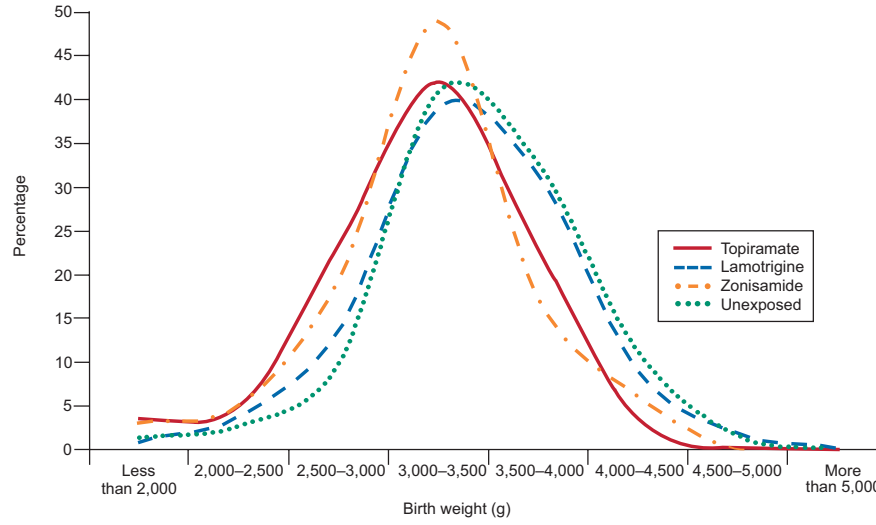

Fig. 2. Birth weight distributions for singleton liveborn neonates exposed to topiramate, zonisamide, and lamotrigine in monotherapy as well as for the unexposed reference group.

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third trimester and 19.3% for those who continue its use later in pregnancy (P=.060); the corresponding prevalences for lamotrigine were 8.1% and 6.7%, respectively. The mean daily doses during pregnancy were 349 mg for lamotrigine, 198 mg for topiramate, and 303 mg for zonisamide. There was no apparent dose effect on the prevalence of SGA for topiramate or zonisamide at the dose ranges used in our population, although the prevalence of SGA was 12.0% for mean topiramate doses less than 50 mg (n=59) and 18.4% for higher doses (P=.273). Regarding polytherapies, the prevalence of SGA was 10.7% for lamotrigine, plus any other anticonvulsant, 18.3% for topiramate, and 14.9% for zonisamide (not mutually exclusive categories).

DISCUSSION

In adults, both topiramate and zonisamide reduce body weight.[1–7,12–14] For both drugs, several mechanisms of action have been proposed, including reductions in appetite and stimulation of energy expenditure.[12,22] However, the ultimate physiologic mechanisms remain unkown.[22] In utero, low doses of topiramate reduce fetal body weight in rats; and in humans, first the small study of Ornoy et al[17] and now ours suggest that exposure during pregnancy to topiramate reduces birth weight without decreasing length of pregnancy. The present study also suggests an association for prenatal zonisamide exposure and low birth weight in humans. It is postulated that the effect of these drugs on fetal growth might be secondary to effects on maternal caloric intake or, more likely, direct effects on fetal fat deposition.[11]

In general, SGA newborns have an increased risk of morbidity and mortality in the perinatal period as well as later in life, including neurodevelopmental handicaps, chronic respiratory impairments, cardiovascular

Table 2. Prevalence of Small for Gestational Age, Low Birth Weight, and Preterm Delivery Among Singleton Liveborn Neonates Exposed to Specific Antiepileptic Drugs in Monotherapy During Pregnancy

Outcome*	Unexposed (n=457)	Lamotrigine (n=1,581)	Topiramate (n=347)	Zonisamide (n=98)
Child's birth weight (g)	3,458.3±517.8	3,402.1±529.3	3,180.8±519.8†	3,200.3±544.0†
Gestational age (wk)	39.3±1.8	39.2±1.7	39.1±2.0, NS	39.2±2.2, NS
Child's length (cm)	51.2±3.4	50.9±3.1	49.8±3.3†	49.9±3.1†
Head circumference (cm)	34.5±1.4	34.6±2.2	34.1±1.5, NS	32.9±5.0, NS
LBW	18 (4.0)	74 (4.7)	29 (8.4)†	8 (8.2), NS
Preterm	27 (5.9)	119 (7.5)	36 (10.4), NS	10 (10.2), NS
SGA	23 (5.0)	107 (6.8)	62 (17.9)†	12 (12.2)‡

NS, not significant; LBW, low birth weight; SGA, small for gestational age.
Data are mean±standard deviation or n (%).
* Nine patients had missing values for birth weight and were not included in these analyses. Ninety-four participants had missing values for birth length. Results for head circumferences are based on 10–15% of the sample.
† P<.01 compared with both lamotrigine and unexposed reference groups.
‡ P<.05 compared with both lamotrigine and unexposed reference groups.

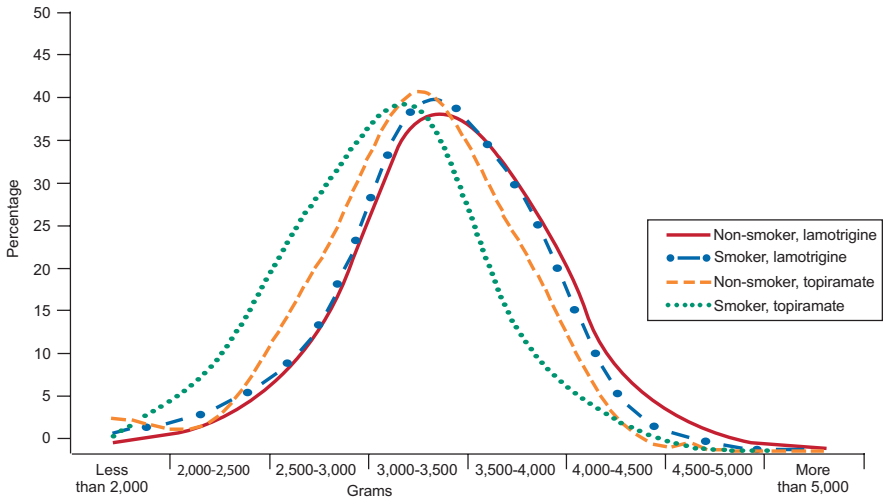

Fig. 3. Birth weight distributions for singleton liveborn neonates exposed to topiramate and lamotrigine in monotherapy stratified by maternal smoking during pregnancy.

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and renal complications, and infections.[23–25] The long-term consequences of topiramate or zonisamide-related SGA are unknown.

Whether the associations found in this nonrandomized study are causal or the result of unbalanced risk factors among users of specific antiepileptic drugs deserves some discussion. Our results do not seem to be explained by smoking, prepregnancy maternal weight, or the underlying indication for these drugs. Because smokers are known to have smaller neonates[24,26] and topiramate users in our population smoked more than the reference group, it is conceivable that our findings could be partially explained by unbalanced maternal smoking in the two groups. However, the association between topiramate and zonisamide with SGA remained after restriction to nonsmokers. Thus, our findings strongly suggest that there is an independent and additive effect of smoking and topiramate leading to a shift in the birth weight curve toward lower values.

We were not able to adjust for maternal weight, also known to be associated with fetal growth,[24,26] because the information had not been systematically collected by the Registry during earlier study years. However, based on data from the U.S. National Health and Nutrition Examination Survey,[27] women of childbearing age using topiramate during the study period years were more frequently overweight than those using other antiepileptic drugs, presumably because topiramate was preferentially prescribed to overweight women seeking its weight loss effect. Thus, adjustment for maternal weight likely would have resulted in larger RR estimates, ie, we may have underestimated the effect of topiramate.

It was reassuring to find similar results when we used an unexposed comparison group without epilepsy. However, hypothetically, there could be a genetic predispositions to both epilepsy and having SGA neonates. Comparisons among different antiepileptic drugs and restriction to women with epilepsy in our analyses minimize this potential confounding by indication, yet there could be residual confounding if different types of epilepsy were associated with fetal weight gain or weight loss. Similarly, although unlikely given the robustness of the estimates to multivariate adjustment, residual confounding by socioeconomic status is plausible.

Table 3. Relative Risk and 95% Confidence Interval of Small for Gestational Age Among Singleton Liveborn Neonates Exposed to the Topiramate and Zonisamide Compared With Those Exposed to Lamotrigine

Outcome	Unexposed (n=457)	Lamotrigine (n=1,581)	Topiramate (n=347)	Zonisamide (n=98)
SGA, n (%)	23 (5.0)	107 (6.8)	62 (17.9)	12 (12.2)
Crude RR (95% CI)		Reference	2.6 (2.0–3.5)	1.8 (1.0–3.2)
Adjusted RR (95% CI)		Reference	2.4 (1.8–3.3)	1.6 (0.9–2.8)
Crude RR (95% CI)	Reference		3.6 (2.2–5.6)	2.4 (1.3–4.7)
Adjusted RR (95% CI)	Reference		3.5 (2.1–5.7)	2.2 (1.1–4.4)

SGA, small for gestational age; RR, relative risk; CI, confidence interval.
Adjusted for maternal age, parity, smoking, education, and periconceptional folic acid.

The North American Antiepileptic Drug Pregnancy Registry relies on self-enrolled volunteers, who may be better functioning, with less severe epilepsy, and might have lower risk of SGA neonates than the general population of women with epilepsy in the United States and Canada. In fact, the reference group of friends and family members enrolled in the Registry had a lower prevalence of SGA than that expected in the general population (ie, 10%). We can only assume that the RRs for specific antiepileptic drugs observed in our study would be similar in the population of exposed pregnant women from whom the sample was drawn. Finally, we did not have a sample large enough to assess dose and duration effects. However, results suggest that topiramate exposure during the second half of the pregnancy and at larger doses might be most relevant.

In conclusion, we found a decrease in mean birth weight and mean birth length among newborns exposed to topiramate and zonisamide in utero compared with those exposed to lamotrigine and with neonates in the unexposed comparison group. Given that many adults taking topiramate lose weight, it is possible that the decreased birth weights seen in our study are mediated by a similar physiologic mechanism. Currently, weight loss treatment regimens combining phentermine and topiramate[6] are being used by young women who might become pregnant. Although there are beneficial effects of lowering weight, and therefore the complications of obesity during pregnancy, before prescribing topiramate, zonisamide, or topiramate and phentermine combinations to women who are pregnant or of childbearing age, the possible risks to a developing fetus, viz., the increased occurrence of oral clefts[8–10] and fetal growth reduction shown to be associated with the topiramate component, should be considered.

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