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Use of topiramate in pregnancy and risk of oral clefts

Andrea V Margulis, MD ScD[1], **Allen A Mitchell, MD**[2], **Suzanne M Gilboa, PhD**[3], **Martha M Werler, ScD**[2], **Murray A Mittleman, MD DrPH**[1,4], **Robert J Glynn, ScD**[5], **Sonia Hernandez-Diaz, MD DrPH**[1], and **National Birth Defects Prevention Study**

[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA, US

[2]Slone Epidemiology Center at Boston University, Boston, MA, US

[3]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, US

[4]Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, Boston, MA, US

[5]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, US

Abstract

Objective—To evaluate the association between monotherapy topiramate use in pregnancy and cleft lip with or without cleft palate (CL/P) in the offspring.

Study design—Data from the Slone Epidemiology Center Birth Defects Study (BDS) from 1997–2009 and the National Birth Defects Prevention Study (NBDPS) from 1997–2007 were analyzed. Conditional logistic regression was used to compare first-trimester use of topiramate monotherapy to no antiepileptic drug use during the periconceptional period between mothers of infants with CL/P and mothers of controls for each study separately, and in pooled data.

Corresponding author, Andrea V Margulis, Harvard School of Public Health, Department of Epidemiology, 677 Huntington Avenue, Kresge Building, Boston, MA 02115, USA, Tel.: +1 617 792 0861, Fax: +1 617 566 7805, andreamargulis@post.harvard.edu.

Potential conflicts of interest

Dr. Margulis reported that the Pharmacoepidemiology program at Harvard School of Public Health, which granted her a student stipend, receives funds for training grants for students from Pfizer and Asisa. The North American AED Pregnancy Registry, to which Dr. Hernandez-Diaz devotes less than 5% of her time, received grants from multiple pharmaceutical companies. Dr. Mitchell reported having Johnson & Johnson stock currently valued at <$20,000. Drs. Mitchell, Werler, Glynn, and Hernandez-Diaz have consulted for or received grants from pharmaceutical companies whose medications are not the subject of this analysis.

Previous presentations

This manuscript has never been published in whole or in part and is not under revision or in press by other journals. An abstract of an earlier version has been presented in the 27th International Conference on Pharmacoepidemiology and Risk Management, organized by the International Society of Pharmacoepidemiology, held in Chicago, IL, on August 15, 2011. These findings were presented at the US Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee meeting held in Silver Spring, MD, on February 22, 2012, where the risks and benefits of the topiramate-containing product to treat obesity and related conditions Qnexa (Vivus Inc., Mountain View, California) were discussed.

Disclaimers

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Results—BDS contained 785 CL/P cases and 6,986 controls; NBDPS contained 2,283 CL/P cases and 8,494 controls. The odds ratios (exact 95% confidence intervals) for the association between topiramate use and CL/P were 10.1 (1.1; 129.2) in BDS, 3.6 (0.7; 20.0) in NBDPS, and 5.4 (1.5; 20.1) in pooled data.

Conclusions—First-trimester use of topiramate may be associated with CL/P.

Keywords

Antiepileptic drugs; Birth defects; Cleft lip; Oral clefts; Topiramate

INTRODUCTION

Approximately 0.5% of pregnant women in the US have epilepsy. [1] Unless the patient has been free of seizures for 2–5 years, the current recommendation is to continue antiepileptic therapy throughout pregnancy to avoid seizures that can cause hypoxic damage to the fetus and maternal morbidity and mortality. [2] Older antiepileptics, such as phenytoin, phenobarbital and valproic acid, carry an increased risk for various specific congenital malformations. [3–5] However, little is known about the fetal safety of the increasingly-used newer antiepileptics. [6–8]

Topiramate was approved in the US for the treatment of generalized tonic-clonic and partial seizures in 1996 and for prevention of migraine in 2004 (the prevalence of migraine peaks at childbearing age in women). [9] In 2006, a generic version was introduced in the US market. Off-label uses include conditions that are also prevalent among women of reproductive age: sleep [10,11] and eating disorders, [12] other psychiatric conditions [13,14] and weight loss. [12]

Animal studies reported an increased risk of craniofacial defects in litters exposed in utero to low doses of topiramate, and other malformations and low birth weight at higher doses. [15] Some postmarketing studies in pregnant women have suggested an increased risk in birth defects overall and, possibly, an increased risk in cleft lip with or without cleft palate (CL/P); however, evidence is inconclusive because neither the exposure nor oral clefts are frequent. [7,16–19] The replication of these findings in large case-control studies, using methods suitable for small sample sizes is critical.

We therefore conducted a matched case-control analysis to evaluate the risk of oral clefts in infants exposed to topiramate during the first trimester of pregnancy, using data from two large congenital malformations case-control studies in North America. We report both study-specific and pooled results.

MATERIALS AND METHODS

Data sources and study populations

The Boston University Slone Epidemiology Center Birth Defects Study (BDS) and the Centers for Disease Control and Prevention's (CDC) National Birth Defects Prevention Study (NBDPS) share several features related to study design, data collection, case classification, and analyses, which have been described in detail elsewhere. [20–24] Both studies include infants with major congenital malformations as cases and infants with no malformations as controls. Pre-pregnancy and pregnancy exposure information is collected after delivery by means of a detailed computer-assisted telephone interview conducted in English or Spanish. Questions focus on maternal medical history and details of medication use and other exposures from two (BDS) or three (NBDPS) months prior to and through the end of pregnancy. Specifically, the questionnaires in both studies inquire about the presence

of seizures or epilepsy and its treatment prior to and during pregnancy. To avoid duplication of participants, the BDS does not enroll women who are in the same catchments as NBDPS subjects. BDS subjects included women with conception dates from May 1997 to July 2009 and the NBDPS included women with expected due dates from October 1997 to December 2007.

During the study period, the BDS recruited mothers of fetuses, stillborn and liveborn infants with malformations and infants without malformations in the greater metropolitan areas of Philadelphia, San Diego and Toronto and portions of Massachusetts and New York. Starting in 1998, subjects also included a random sample of all births without congenital malformations in Massachusetts as controls. To identify study subjects, BDS staff regularly review admissions and discharge records of birth centers, community hospitals and pediatric clinics; subjects are also identified from the birth defects registries in Massachusetts and New York. Interviews are conducted within 6 months of delivery. [20–22] Infants with chromosomal abnormalities, single-gene conditions, and malformations associated with amniotic bands were excluded from the present study. The BDS is HIPAA-compliant and is approved by the relevant institutional review boards.

To ascertain cases, the NBDPS utilizes the birth defects surveillance systems of Arkansas, California, Georgia (Metropolitan Atlanta Congenital Defects Program operated by CDC), Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas and Utah, covering an annual birth population of more than 482,000 (approximately 10% of births in the US). Eligible subjects include liveborn infants with major congenital malformations and with no accompanying chromosomal abnormalities or single-gene conditions. Most states included stillborn infants and terminations with major congenital malformations, with the exception of New Jersey, which did not include either, and Massachusetts, which did not include terminations. Controls are liveborn infants with no major malformations randomly selected from birth certificates or hospital discharge data from the participating states. Interviews are conducted between 6 weeks and 24 months after the estimated date of delivery. [22–24] The NBDPS is HIPAA-compliant and approved by the institutional review boards of the CDC and all participating study centers.

Exposure ascertainment

First-trimester exposure was defined as the use of topiramate in the first 90 days after the conception date (“first trimester”). To avoid confounding by other antiepileptic drugs, the analysis was restricted to topiramate monotherapy, defined as no use of other antiepileptic drugs in the first trimester. Information on dose and indication was available in BDS data.

Outcomes

Both data sources define major congenital malformations as structural malformations with medical, surgical or cosmetic relevance. In both studies, information on the presence of congenital malformations is obtained from hospital discharges and medical records and experts review and classify each identified birth defect. Undescended testis, patent foramen ovale or patent ductus arteriosus in newborns of less than 37 completed weeks of gestational age at birth are not included in analyses of either data set. The current study focused on cases diagnosed with CL/P, as this was the specific malformation hypothesized to be associated with topiramate in previous postmarketing studies. Because some shared risk factors have been identified, [25] we also planned to separately consider risks for cleft palate alone (CP). However, there were no infants with CP exposed to topiramate in either study, so no further analysis was conducted.

Statistical analyses

Main analysis—We used conditional logistic regression to compare the use of topiramate monotherapy in the first trimester to no antiepileptic use in the 60 days prior to conception or in the first 90 days of pregnancy. All odds ratios (ORs) are reported with exact 95% confidence intervals. The analysis focused on major congenital malformations as a group (including oral clefts) and separately on CL/P with or without other major congenital malformations. In the study-specific primary analyses, matched sets were formed on the basis of year (2-year categories) and region (California, Massachusetts, New York, Pennsylvania, and Ontario for BDS and Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah for NBDPS) of birth, to account for potential differences in case selection that might have been introduced across regions and time. Matched sets contained as many cases and controls as were available per stratum. In analyses on pooled data, matched sets were formed on the basis of year and region of birth and study (BDS and NBDPS).

Confounding factors—Given the small number of exposed subjects involved in the analyses, it would be inappropriate to attempt to control confounding by traditional multivariable approaches. Instead, in our secondary analyses, to assess potential confounding by characteristics beyond year and region of birth, we repeated the conditional logistic regression analysis in the pooled data on new matched sets. To form these sets, we matched in this analysis case infants to control infants on year and region of birth, study, and one more variable at a time from the following *a priori* defined list: maternal race/ethnicity, family history of oral clefts (first-degree relatives with CL/P or CP), maternal age at conception (age less than 25, [25; 30), [30; 35), 35 years and over), prepregnancy maternal body mass index (BMI; less than 18.5 kg/m^2, [18.5; 25), [25; 30), 30 and over), first-trimester cigarette smoking, first-trimester alcohol consumption, diagnosis of epilepsy, diagnosis of diabetes or gestational diabetes prior to or during the index pregnancy, and folic acid supplementation from single-ingredient or folic-acid containing multivitamin products (any use in the 2 months prior to the beginning of pregnancy or the first 2 months of pregnancy).

Dose and indication—We identified daily dose and indication among infants with CL/P and among controls from BDS.

Analyses were performed in SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Slone Birth Defects Study

The study population consisted of 6,983 controls and 10,618 infants with major congenital malformations (the latter excluded 2,594 infants with chromosomal abnormalities, single-gene inherited diseases, malformations associated with amniotic bands, syndromic or metabolic disorders). Among the infants with malformations, 785 had CL/P. Maternal and offspring characteristics of CL/P cases and controls are presented in Table 1. Five infants with malformations were exposed to topiramate monotherapy, of which 3 had CL/P; 2 of the controls were exposed to topiramate. The OR comparing first-trimester exposure to topiramate monotherapy to no antiepileptic drug use for major congenital malformations was 1.22 (0.19; 13.01) and for CL/P was 10.13 (1.09; 129.21) (Table 2).

The daily dose and indication of topiramate among cases of CL/P were 25 mg (migraine) and 100 mg (epilepsy); the third case mother, who took the drug for depression, did not

report dose. The 2 control infants were both exposed to a daily dose of 100 mg for migraine prophylaxis.

National Birth Defects Prevention Study

The study population consisted of 8,494 controls and 23,333 case infants. Of them, 2,283 had CL/P. Maternal and offspring characteristics of CL/P cases and controls are presented in Table 1. Ten case infants, including 4 infants with CL/P, and 4 control infants received first-trimester monotherapy exposure to topiramate. The OR comparing first-trimester exposure to topiramate and no antiepileptic drug use for major congenital malformations was 0.92 (0.26; 4.06) and for CL/P was 3.63 (0.66; 20.00). The mothers of 2 infants with major congenital malformations (1 of them with CL/P) and of 1 control infant reported having been diagnosed with epilepsy.

Pooled data

Among the pooled study population, first-trimester monotherapy exposure to topiramate was not associated with an increase in the risk of major congenital malformations overall (OR 1.01 [0.37; 3.22]), but it was associated with an elevated risk of CL/P (OR 5.36 [1.49; 20.07)]. Point estimates and confidence intervals were not substantially modified by matching on any additional characteristic in the analyses of either major congenital malformation (OR point estimates varied between 0.91 and 1.03) or CL/P (OR point estimates varied between 4.01 and 5.92) (data not shown).

COMMENT

Monotherapy topiramate use during the first trimester of pregnancy was associated with an increased risk of CL/P as compared to no use of antiepileptics in pooled data from BDS and NBDPS.

Topiramate has effects on multiple physiologic pathways. It affects cell polarization through effects on various ion channels; it also inhibits the carbonic anhydrase [12,26] and histone deacetylases; histone deacetylases are also inhibited by valproic acid. [27] Litters born to pregnant rodents exposed to doses equivalent to 50% of the recommended human dose for epilepsy, or below, had an increased incidence of craniofacial defects (mice), low birth weight (mice and rats) or other structural variations (rats). [15] Rabbits were only affected at high doses.

In humans, a number of results, each based on a small number of exposed subjects, collectively suggest that the risk of major malformations is not increased or not largely so, but that the risk of CL/P may be elevated. Our findings support these results. In 2008, Hunt et al. reported an incidence of CL/P 11 times the background rate for topiramate-exposed infants in monotherapy, based on 2 cases among 70 exposures from the UK Epilepsy and Pregnancy Register; there were 3 infants with major congenital malformations in total.[18] In the same year, Ornoy et al. reported 1 infant with a major congenital malformation (not an oral cleft) among 29 women exposed to topiramate monotherapy using the Israeli Teratology Service data.[17] In 2010, Hernández-Díaz et al. reported in an abstract 4 cases of cleft lip in 289 infants exposed in monotherapy in the first trimester in the North American Antiepileptic Drug Pregnancy Registry, which represented an elevated risk compared to an external reference population. [19] These results were used by the U.S. Food and Drug Administration in March 2011, to reclassify topiramate from pregnancy category C to pregnancy category D. [28] Further information has been presented subsequent to these reports. In a population-based Danish cohort focused on newer antiepileptic medications, Molgaard-Nielsen et al. identified 108 first-trimester topiramate-exposed pregnancies,

among which there were 5 born with malformations; while they reported no significant increase in overall risk (OR = 1.44), it is of interest that one of the malformed infants had a CL/P (an absolute risk of 1% with wide confidence intervals). [7] Additional reports, available only as abstracts, include a study by Day et al. [29] that reported almost identical risks of major congenital malformations in infants with topiramate monotherapy exposure in utero and infants born from untreated epileptic women, using pooled data from a variety of international sources, overlapping with some of the above (relative risk = 1.03). Pack et al.[30] reported no association between topiramate use in the 10 months prior to delivery and either major congenital malformations or oral clefts, relative to users of other antiepileptic drugs (relative risk for major congenital malformations = 1.18; for oral clefts, 1.26) and women with epilepsy who were not receiving topiramate (relative risk for major congenital malformations = 0.87; for oral clefts, 0.85), using commercial claims data from the US.

To our knowledge, no other specific malformations have been associated with topiramate. While our findings do not suggest that topiramate increases the risk of malformations overall, we considered only one hypothesis related to specific malformations—CL/P. Although we observed no increased risk for other major malformations as a group, we cannot exclude the possibility that topiramate may be related to a modest increase in one or more specific defects.

Though we were unable to perform a full dose-response analysis, our limited results do not suggest a threshold effect on infants born with CL/P, since one case was exposed to the low dose of 25 mg/d for migraine prevention.

Several antiepileptic drugs (e.g., valproic acid, carbamazepine, phenytoin, phenobarbital, lamotrigine) have been associated with an increased risk of specific congenital malformations (e.g., oral clefts, neural tube defects, heart defects, hypospadias, craniosynostosis, polydactyly). [4,5,31–33] A dose-related risk for major congenital malformations overall has been reported for valproic acid, phenobarbital, lamotrigine and carbamazepine, [34,35] though consistently replicated only for valproic acid.[36,37] There is disagreement on whether antiepileptic drugs or epilepsy itself are responsible for the congenital malformations found in the infants born to epileptic women who are on antiepileptic treatment. Studies reported that epileptic women who do not use antiepileptic drugs during pregnancy are not at a higher risk of delivering affected infants than non-epileptic women who were not exposed to antiepileptic medications. [3,5,38] However, residual confounding by epilepsy severity is generally difficult to rule out, as severe, active epilepsy rarely remains untreated. In this study, epilepsy was reported by less than half of topiramate users. Epilepsy was a weak confounder; we could not assess the impact of seizures in pregnancy on congenital malformations. To our knowledge, no reports have suggested an association between migraine and congenital malformations. The vasoactive drug ergotamine, used to treat migraine crises, is contraindicated in pregnancy because of its risk of fetopathy, [39] but none of the women exposed to topiramate in our study reported exposure to ergotamine.

Despite our use of data from two large birth defects case-control studies, the main limitation of this analysis is its low number of exposed cases and exposed controls. For this reason, even though we applied methods that are appropriate for small cell counts, our ability to control for confounding is limited. We matched on data collection-related factors in all analyses and assessed other potential confounders individually, but we could not assess confounding by combinations of these or conduct stratified analyses due to the paucity of data. The differences in effect size for topiramate and CL/P between the BDS and NBDPS may be due to sampling variability, different amounts of residual confounding or varying underlying risk.

Our results must be interpreted in light of several additional limitations: recall bias is a potential limitation of this study, as exposure information is collected after the pregnancy outcome is known. To diminish the potential for bias, the computer-assisted interview is scripted, ensuring identical questions are asked to mothers of case and control infants. Recall is enhanced by presenting the interviewees with a list of medications and illnesses in the script. Some studies have attempted to diminish the risk of recall bias by comparing infants with the malformation of interest to infants with malformations unrelated to the exposure. In this study, we did not use such a comparison group because the safety pattern of topiramate is not yet well characterized. However, the fact that we found an association with only the *a priori* hypothesized malformation (i.e., CL/P) and not with overall malformations argues against recall bias.

Pregnancies terminated because of congenital malformations in the fetus are eligible for inclusion in BDS and in most of the participating states in NBDPS. Neither data source identifies the presence of congenital malformations in spontaneous abortions less than 20 gestational weeks. This potential underascertainment of major congenital malformations would bias risk estimates towards the null. However, CL/P is not lethal and we do not expect substantial underascertainment of CL/P in the absence of associated syndromes or chromosomal abnormalities.

In conclusion, the results of our pooled analysis are consistent with recent reports of an increased risk of CL/P associated with the use of topiramate in the first trimester of pregnancy. However, the absolute risk should be kept in perspective. Approximately 1 in 1,000 infants is born with CL/P; [40,41] assuming our results are valid and accurate, our observed pooled OR of approximately 5 would translate into a risk in the order of 5/1,000 for any individual topiramate-exposed pregnancy. Clinical decision-makers should weigh the risks of treatment with topiramate against the risks of alternative therapeutic choices, as well as the comparative effectiveness of topiramate and alternative treatments.

Acknowledgments

Coding of drug information in the NBDPS used the Slone Drug Dictionary under license from the Slone Epidemiology Center at Boston University.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1

Maternal and offspring characteristics of study participants, Slone Birth Defects Study (1997–2009) and National Birth Defects Prevention Study (1997–2007).

Characteristics	Slone Birth Defects Study		National Birth Defects Prevention Study	
	Infants without malformations N = 6,983	Infants with CL/P N = 785	Infants without malformations N = 8,494	Infants with CL/P N = 2,283
Maternal age in years, mean (SD)	29.3 (5.9)	28.5 (6.1)	27.3 (6.1)	27.0 (6.1)
Prepregnancy BMI in kg/m^2, N (%)				
Less than 18.5	207 (3.0)	38 (4.8)	439 (5.2)	150 (6.6)
[18.5; 25)	3,964 (56.8)	379 (48.3)	4,180 (49.2)	1,069 (46.8)
[25; 30)	1,564 (22.4)	173 (22.0)	2,033 (23.9)	504 (22.1)
[30; 35)	566 (8.1)	75 (9.6)	912 (10.7)	255 (11.2)
35 and over	327 (4.7)	52 (6.6)	564 (6.6)	182 (8.0)
Maternal race/ethnicity, N (%)				
Non-Hispanic White	4,917 (70.4)	507 (64.6)	5,004 (58.9)	1,376 (60.3)
Non-Hispanic Black	538 (7.7)	65 (8.3)	959 (11.3)	139 (6.1)
Hispanic	997 (14.3)	124 (15.8)	1,975 (23.3)	609 (26.7)
Asian/Pacific Islander	386 (5.5)	71 (9.0)	250 (2.9)	59 (2.6)
Native American/Alaskan Native	NA	NA	43 (0.5)	19 (0.8)
Other	139 (2.0)	15 (1.9)	260 (3.1)	81 (3.5)
Maternal education in years, N (%)				
Less than or 13	1,936 (27.7)	287 (36.6)	3,446 (40.6)	1,106 (48.4)
[13; 15]	1,635 (23.4)	195 (24.8)	2,260 (26.6)	583 (25.5)
16 and over	3,409 (48.8)	303 (38.6)	2,637 (31.0)	573 (25.1)
First-degree relative with CL/P or CP	31 (0.4)	56 (7.1)	29 (0.3)	126 (5.5)
Diabetes, N (%)	365 (5.2)	67 (8.5)	559 (6.6)	204 (8.9)
Periconceptional folic acid supplementation, N (%)	6,087 (87.2)	640 (81.5)	6,282 (74.0)	1,654 (72.4)
Any smoking in first trimester, N (%)	1,150 (16.5)	174 (22.2)	1,350 (15.9)	494 (21.6)
Any alcohol use in first trimester, N (%)	2,754 (39.4)	257 (32.7)	3,087 (36.3)	850 (37.2)

CL/P: cleft lip with or without cleft palate – CP: cleft palate – BMI: body mass index – NA: category not available

Note: Missing data among non-malformed infants and infants with CL/P: Slone Birth Defects Study: 423 subjects did not report their BMI, 9 subjects did not report race/ethnicity, 3 did not report years of education, 262 did not report on smoking status and 37 did not report on alcohol intake; National Birth Defects Prevention Study: 489 subjects did not report their BMI, 3 subjects did not report race/ethnicity, 172 did not report years of education, 144 did not report on smoking status.

Table 2

Use of topiramate in monotherapy in the first trimester of pregnancy and risk of major congenital malformations and CL/P, Slone Birth Defects Study (1997–2009) and National Birth Defects Prevention Study (1997–2007).

Use of antiepileptic drugs	Infants without malformations	Infants with major congenital malformations [a]		Infants with CL/P	
	N	N	OR (95% CI)	N	OR (95% CI)
Slone Birth Defects Study [b]					
No use of antiepileptic drugs [c]	6,933	10,503	Reference	778	Reference
Topiramate monotherapy in first trimester	2	5	1.22 (0.19 – 13.01)	3	10.13 (1.09 – 129.21)
National Birth Defects Prevention Study [b]					
No use of antiepileptic drugs	8,434	23,102	Reference	2,256	Reference
Topiramate monotherapy in first trimester	4	10	0.92 (0.26 – 4.06)	4	3.63 (0.66 – 20.00)
Pooled data [d]					
No use of antiepileptic drugs	15,367	33,605	Reference	3,034	Reference
Topiramate monotherapy in first trimester	6	15	1.01 (0.37 – 3.22)	7	5.36 (1.49 – 20.07)

CL/P: cleft lip with or without cleft palate – OR: odds ratio – 95%CI: 95% confidence interval

[a] The major congenital malformations found in topiramate-exposed infants were left cleft lip, right cleft lip and cleft palate, unilateral cleft lip and palate (unspecified side), cleft lip (not otherwise specified), bilateral cleft lip, bilateral cleft lip and palate, left Bochdalek diaphragmatic hernia, patent ductus arteriosus, patent foramen ovale, atrial septal defect (ostium secundum type), unspecified atrial septal defect, unspecified ventricular septal defect, coarctation of the aorta, pulmonary valve stenosis, unspecified brain anomalies, spina bifida, and anal atresia with fistula.

[b] Analyses conditional on year and region of birth.

[c] No AED use refers to no use of antiepileptic drugs in the 2 months prior to pregnancy or in the first trimester of pregnancy

[d] Analyses conditional on year and region of birth, and study.