

# Newer-Generation Antiepileptic Drugs and the Risk of Major Birth Defects

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**T**HE PREVALENCE OF ANTIEPILEPTIC drug use in pregnant women is 0.2% to 0.5%.<sup>1-3</sup> While their main indication is epilepsy, antiepileptic drugs are increasingly being used in the treatment of bipolar mood disorders, migraine, and neuropathic pain syndrome.<sup>4</sup> In Denmark, approximately half of all such prescriptions were for epilepsy in 2002,<sup>5</sup> and it has been estimated to be the same in the United States.<sup>6</sup> Use of older-generation antiepileptic drugs such as phenobarbital, phenytoin, valproate, and carbamazepine during pregnancy has been associated with an approximately 3-fold increased risk of birth defects.<sup>7</sup> Since the 1990s, options for antiepileptic drug treatment have substantially increased.<sup>8</sup>

However, there is only sparse information on the teratogenic effects of most of the newly licensed antiepileptic drugs. Among pregnant women with epilepsy, lamotrigine was the most commonly prescribed antiepileptic drug in Denmark from 1996 through 2000,<sup>9</sup> and among the 2 most commonly used antiepileptic drugs in the United States from 1999 through 2004.<sup>10</sup> Observational studies of the teratogenic effect of lamotrigine have been conducted.<sup>4,11</sup> However, the safety data are primarily based on different types of pregnancy registries with voluntary enrollment and often lack valid comparison groups.<sup>12-15</sup> For levetiracetam, topiramate, oxcarbazepine, and gabapentin, the available

**Context** Epilepsy during pregnancy is a therapeutic challenge. Since the 1990s, the number of licensed antiepileptic drugs has substantially increased, but safety data on first-trimester use of newer-generation antiepileptic drugs and birth defects are limited.

**Objective** To study the association between fetal exposure to newer-generation antiepileptic drugs during the first trimester of pregnancy and the risk of major birth defects.

**Design, Setting, and Participants** Population-based cohort study of 837 795 live-born infants in Denmark from January 1, 1996, through September 30, 2008. Individual-level information on dispensed antiepileptic drugs to mothers, birth defect diagnoses, and potential confounders were ascertained from nationwide health registries.

**Main Outcome Measures** Prevalence odds ratios (PORs) of any major birth defect diagnosed within the first year of life by fetal exposure to antiepileptic drugs.

**Results** Of the 1532 infants exposed to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam during the first trimester, 49 were diagnosed with a major birth defect compared with 19911 of the 836 263 who were not exposed to an antiepileptic drug (3.2% vs 2.4%, respectively; adjusted POR [APOR], 0.99; 95% confidence interval [CI], 0.72-1.36). A major birth defect was diagnosed in 38 of 1019 infants (3.7%) exposed to lamotrigine during the first trimester (APOR, 1.18; 95% CI, 0.83-1.68), in 11 of 393 infants (2.8%) exposed to oxcarbazepine (APOR, 0.86; 95% CI, 0.46-1.59), and in 5 of 108 infants (4.6%) exposed to topiramate (APOR, 1.44; 95% CI, 0.58-3.58). Gabapentin (n=59) and levetiracetam (n=58) exposure during the first trimester was uncommon, with only 1 (1.7%) and 0 infants diagnosed with birth defects, respectively.

**Conclusion** Among live-born infants in Denmark, first-trimester exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam compared with no exposure was not associated with an increased risk of major birth defects.

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safety data are even more sparse.<sup>14,16-18</sup> Together with lamotrigine, the first 3 of these drugs were among the most commonly used antiepileptic drugs in women of childbearing age in the United States in 2007,<sup>10</sup> and more information is needed regarding the effects of these drugs during pregnancy.

We conducted a nationwide cohort study of all live births in Denmark from January 1996 through September 2008 using Danish health registries. Our

primary objective was to study the association between the use of lamotrigine, oxcarbazepine, topiramate, gabapentin, and levetiracetam (newer-generation antiepileptic drugs) during the first trimester of pregnancy

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and the risk of any major birth defects.

## METHODS

The Medical Birth Registry was established in 1978 and contains records on all Danish births.<sup>19</sup> The records include the personal identification number (a 10-digit number assigned to all Danish residents) of the parents and the newborn, date of birth, indication of single vs multiple births, gestational age, vital status, and other physical characteristics of the newborn. We constructed a study cohort of all live births from January 1, 1996, through September 30, 2008, using the Medical Birth Registry. The onset of pregnancy was defined as the first day of the last menstrual period and was estimated by subtraction of the gestational age from the date of birth.

Recording of gestational age in the Medical Birth Registry is based on self-report of the first day of the last menstrual period and in most women this date is corrected by prenatal ultrasound.<sup>20</sup> A previous study validated the gestational age registration in the Medical Birth Registry by comparing the registered data with the medical records. The study found concordance in 87% of the cases when agreement was defined as within 1 week.<sup>21</sup> In births with a missing gestational age (0.9%), we imputed the cohort median of 280 days. The study was approved by the Danish Data Protection Agency. Ethics approval was not required for registry-based research in Denmark.

### Antiepileptic Drug Exposure

Information on filled prescriptions of antiepileptic drugs was obtained from the Registry of Medicinal Product Statistics, which contains individual-level data on all prescriptions dispensed at Danish pharmacies since 1994. Each pharmacy record comprises the personal identification number of the patient, date the prescription was filled, type of drug according to the Anatomical Therapeutic Chemical (ATC) classification system, number of packets or units of the product

code sold, and the number of defined daily doses contained in the prescription.<sup>22</sup> The World Health Organization's defined daily dose for lamotrigine is 300 mg.<sup>23</sup> We included the following types of prescriptions filled by the cohort mothers from the first day of the last menstrual period until birth: lamotrigine (ATC code N03AX09), oxcarbazepine (ATC code N03AF02), topiramate (ATC code N03AX11), gabapentin (ATC code N03AX12), and levetiracetam (ATC code N03AX14).

### Birth Defects

Cases of birth defects were identified through the National Patient Registry covering January 1, 1996, through March 31, 2009. The registry contains individual-level data on all inpatients and outpatients, including the personal identification number, dates of admission and discharge, and diagnoses classified according to the International Classification System of Diseases.<sup>24</sup> Information on major birth defects were defined according to the European surveillance of congenital anomalies (EUROCAT) classification system of subgroups of major congenital anomalies.<sup>25</sup> Minor defects were excluded according to the EUROCAT exclusion list.<sup>26</sup> Further modification of the EUROCAT classification subgroups was made; infants with chromosomal aberrations (n=1614), genetic disorders (n=1323), and birth defects with known causes (n=369) such as fetal alcohol syndrome were identified and excluded from the study cohort (there are more details in the eMethods at <http://www.jama.com>). The National Patient Registry does not include data from the primary care setting and cases in our study are therefore limited to those who were diagnosed at hospitals and in ambulatory care. We included infants diagnosed within the first year of life.

### Potential Confounders

From the Medical Birth Registry, the Central Person Register, and Statistics Denmark, we obtained information on birth year, maternal parity, age at onset of pregnancy, country of origin, place of

residence at the time of pregnancy onset, level of education and socioeconomic status in the year of pregnancy onset, smoking status during pregnancy, and history of birth defects in siblings, which we linked to the cohort. From the National Patient Registry and the Registry of Medicinal Product Statistics, we obtained the following information on maternal diseases and drug exposure that could be associated with both use of antiepileptic drugs and birth defects: maternal epilepsy diagnosed before the second trimester, maternal migraine diagnosed before the second trimester, maternal mood affective disorders diagnosed before the second trimester, filled prescriptions for older-generation antiepileptic drugs during the first trimester, antidepressant drugs, and migraine drugs (the International Classification System of Diseases and ATC classification codes appear in the eMethods). Regarding maternal morbidities, the National Patient Registry does not include diagnoses made by a medical specialist in the primary care setting.

### Statistical Analysis

We used SAS statistical software version 9.1 to perform logistic regression (PROC GENMOD) with the binomial distribution and canonical logit link function (SAS Institute Inc, Cary, North Carolina) to estimate prevalence odds ratios (PORs) with 95% confidence intervals (CIs).<sup>27</sup> The POR is the ratio between the prevalence odds of birth defects in infants from antiepileptic drug-exposed pregnancies and prevalence odds of birth defects in infants from unexposed pregnancies. The selection of potential confounders was based on a pairwise-forward selection process using the change in estimate as the criterion for inclusion in the final models. The potential confounders were individually included in separate models with antiepileptic drug use and selected for the final adjusted regression models if they changed the PORs by 10% or more. Missing values were included as a separate category where applicable when evaluating the change in estimate. No potential confounder had

**Table 1.** Characteristics of Participants in Denmark From January 1, 1996, Through September 30, 2008<sup>a</sup>

	No. (%) of Live-Born Infants (N = 837 795) <sup>a</sup>	
	Exposed to Any Newer-Generation Antiepileptics During First Trimester (n = 1532)	Unexposed (n = 836 263) <sup>b</sup>
Birth range, y		
1996-1998	184 (12)	200 617 (24)
1999-2001	268 (17)	197 915 (24)
2002-2004	401 (26)	192 695 (23)
2005-September 2008	679 (44)	244 684 (29)
Mother's parity		
0	789 (52)	353 243 (42)
1	460 (30)	300 501 (36)
2	184 (12)	115 298 (14)
≥3	63 (4)	43 071 (5)
Unknown	36 (2)	23 798 (3)
Mother's age at onset of pregnancy, y		
<18	6 (0.4)	2309 (0.3)
18-24	224 (15)	112 533 (13)
25-29	515 (34)	291 353 (35)
30-34	545 (36)	295 047 (35)
35-39	210 (14)	116 166 (14)
40-44	29 (2)	17 887 (2)
≥45	3 (0.2)	616 (0.1)
Mother's country or region of origin		
Denmark	1409 (92)	713 839 (85)
Europe and North America	39 (3)	43 335 (5)
Rest of the world	82 (5)	74 663 (9)
Unknown	2 (0.1)	4074 (0.5)
Mother's place of residence in Denmark		
Copenhagen	197 (13)	133 495 (16)
Copenhagen suburbs	133 (9)	72 754 (9)
North Sealand	101 (7)	58 176 (7)
East Sealand	50 (3)	32 590 (4)
West or South Sealand	158 (10)	73 393 (8)
Bornholm	9 (1)	4718 (1)
Funen	116 (8)	68 130 (8)
North Jutland	110 (7)	82 707 (10)
East Jutland	273 (18)	126 217 (15)
West Jutland	172 (11)	64 474 (8)
South Jutland	212 (14)	104 507 (12)
Unknown	1 (0.1)	14 750 (2)
Mother's level of education		
Compulsory school	516 (34)	177 104 (21)
Secondary school	144 (9)	107 684 (13)
Vocational training or short tertiary education	490 (32)	294 639 (35)
Medium or long tertiary education	352 (23)	220 410 (26)
Unknown	30 (2)	36 074 (4)
Mother's socioeconomic status		
Outside labor market	570 (37)	207 804 (25)
Employed with basic or no qualifications	433 (28)	287 977 (34)
Employed with medium-level qualifications	263 (17)	164 219 (20)
Employed with unknown qualifications	89 (6)	51 464 (6)
Self-employed or coworking spouse	32 (2)	20 528 (2)
Top manager	143 (9)	98 344 (12)
Unknown	2 (0.1)	5575 (1)

(continued)

more than 6% missing values and none of these was identified as a confounder using the change-in-estimate approach.

In the primary analyses, our main outcome measure was all major birth defects. In additional preplanned explorative analyses, we investigated subgroups of birth defects ordered by organ system without correction for multiple statistical comparisons. The date that the prescription was filled was considered the date of exposure. The main exposure period of interest was the first trimester of pregnancy (the period in which structural defects are most likely to be caused). Other exposure definitions were explored in the sensitivity analyses.

In a preplanned analysis, we also evaluated the dose-response effects of the mean daily dose of lamotrigine during the first trimester (≤250 mg or >250 mg) on the risk of any major birth defects. The a priori cutoff value of 250 mg/d was based on a previous study.<sup>14</sup> The mean daily dose was estimated as the total number of defined daily doses during the first trimester divided by 84 days, which corresponded to the number of days in that period. Additional post hoc sensitivity analyses were performed excluding multiple births, examining risk by maternal diagnosis, adjusting for teratogenic drugs, and investigating temporal trends. A P value of less than .05 was considered significant.

**RESULTS**

A total of 837 795 live births were included in the study cohort, and among these 19 960 were diagnosed with a major birth defect (2.4%) during the first year of life. Descriptive characteristics of the study population are presented in TABLE 1. Among 1532 pregnancies exposed to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam at any time during the first trimester, 49 infants were diagnosed with a major birth defect (3.2%) compared with 19 911 infants (2.4%) among 836 263 unexposed pregnancies (crude POR, 1.35; 95% CI, 1.02-1.80).

Estimates of the association between the use of any newer-generation anti-epileptic drug during the first trimester and the risk of any major birth defects including potential confounders individually are presented in eTable 1 at <http://www.jama.com>. Maternal use of older-generation antiepileptic drugs during the first trimester and maternal diagnosis of epilepsy before the second trimester were the only covariates that changed the PORs by 10% or more. After adjusting the regression models for these covariates, exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam at any time during the first trimester was no longer associated with an increased risk of major birth defects (adjusted POR, 0.99; 95% CI, 0.72-1.36).

TABLE 2 presents crude and adjusted PORs for any major birth defect according to first-trimester exposure for the 5 newer-generation antiepileptic drugs together and individually. First-trimester use of lamotrigine, the most commonly prescribed newer-generation antiepileptic drug, was not associated with major birth defects after adjustment (adjusted POR, 1.18; 95% CI, 0.83-1.68) as well as oxcarbazepine, topiramate, or gabapentin; however, only relatively few pregnancies were exposed to the latter 2 antiepileptic drugs during the first trimester. However, our estimates suggest that a relative risk of any major birth defect of higher than 3.58 for topiramate and 3.85 for gabapentin can probably be excluded with some certainty.

No infants with any major birth defects were exposed to levetiracetam during the first trimester. Furthermore, there was no dose-response effect of lamotrigine ( $\leq 250$  mg/d or  $> 250$  mg/d) on the risk of any major birth defects after adjustment. There was no difference in the PORs of any major birth defect associated with exposure to any newer-generation antiepileptic drug stratified on older-generation antiepileptic drugs and diagnosis of epilepsy (details appear in the stratified analyses section of the eResults at <http://www.jama.com>).

The FIGURE shows exploratory analyses of associations between first-trimester use of newer-generation antiepileptic drugs and major birth defect subgroups categorized by organ system. There was no significant increased risk of any major birth defect subgroup in infants exposed to any antiepileptic drug during the first trimester. Similar risk estimates were seen when restricting the exposure to la-

motrigine during the first trimester, barring a significant 4.11-fold increased risk of eye defects. However, the explorative analyses were based on a small number of cases and should therefore be interpreted with caution (eTable 2 at <http://www.jama.com> provides a detailed description of the specific defects diagnosed in infants exposed to newer-generation antiepileptic drugs during the first trimester).

**Table 1.** Characteristics of Participants in Denmark From January 1, 1996, Through September 30, 2008 (continued)

	No. (%) of Live-Born Infants (N = 837 795) <sup>a</sup>	
	Exposed to Any Newer-Generation Antiepileptics During First Trimester (n = 1532)	Unexposed (n = 836 263) <sup>b</sup>
Maternal smoking status during pregnancy		
Smoker	330 (22)	160 804 (19)
Unknown status	83 (5)	35 019 (4)
History of birth defects in siblings	77 (5)	39 629 (5)
Maternal diseases diagnosed before second trimester <sup>c</sup>		
Epilepsy	1164 (76)	3337 (0.4)
Migraine	34 (2)	4934 (1)
Any mood affective disorder	28 (2)	1452 (0.2)
Maternal drug exposure during first trimester		
Older-generation antiepileptic	176 (11)	1197 (0.1)
Migraine	19 (1)	4149 (0.5)
Antidepressant	126 (8)	8742 (1)

<sup>a</sup>Percentages may not equal 100% within groupings due to rounding.  
<sup>b</sup>Cohort did not fill any prescriptions of newer-generation antiepileptic drugs at any time during pregnancy.  
<sup>c</sup>Identified in the National Patient Registry, which does not include diagnoses made in the primary care setting.

**Table 2.** Associations Between Newer-Generation Antiepileptic Drug Use During Pregnancy and Major Birth Defects in a Cohort of 837 795 Live Births in Denmark

	Exposure During First Trimester			
	No. of Women <sup>a</sup>	Birth Defects, No. (%)	POR (95% CI)	
			Crude	Adjusted <sup>b</sup>
Newer-generation antiepileptic drugs				
Exposed	1532	49 (3.2)	1.35 (1.02-1.80)	0.99 (0.72-1.36)
Unexposed	836 263	19 911 (2.4)	1 [Reference]	1 [Reference]
Lamotrigine, mg/d	1019	38 (3.7)	1.59 (1.15-2.2)	1.18 (0.83-1.68)
$\leq 250$	766	31 (4.0)	1.73 (1.21-2.48)	1.29 (0.88-1.90)
$> 250$	253	7 (2.8)	1.17 (0.55-2.47)	0.84 (0.39-1.82)
Oxcarbazepine	393	11 (2.8)	1.18 (0.65-2.15)	0.86 (0.46-1.59)
Topiramate	108	5 (4.6)	1.99 (0.81-4.88)	1.44 (0.58-3.58)
Gabapentin	59	1 (1.7)	0.71 (0.10-5.10)	0.53 (0.07-3.85)
Levetiracetam	58	0	Not estimable	Not estimable

Abbreviations: CI, confidence interval; POR, prevalence odds ratio.  
<sup>a</sup>The numbers of women exposed to each individual antiepileptic drug sums to more than 1532 because some of them took more than 1 drug.  
<sup>b</sup>Adjusted for use of older-generation antiepileptic drugs during the first trimester and diagnosis of epilepsy before the second trimester.

We conducted a number of sensitivity analyses to evaluate the robustness of our results, including adjusting for exposure to drugs in the US Food and Drug Administration's pregnancy categories D and X, restricting analyses to women who only used newer-generation antiepileptic drugs during the first trimester, who had first-trimester exposure only to lamotrigine, or who filled any newer-generation antiepileptic drug prescription or a prescription for lamotrigine at 5- to 12-weeks gestation (period of maximal susceptibility), excluding multiple births or women exposed to older-generation antiepileptic drugs, and including those with use of newer-generation antiepileptic drugs only

during the second and third trimesters. No association with major birth defects was found in any of these analyses (the sensitivity analyses section of the eResults at <http://www.jama.com> provides more detail).

We also examined the risk of any major birth defects by maternal diagnosis as a proxy for indication, adjusted only for maternal exposure to older-generation antiepileptic drugs during the first trimester. The PORs for any major birth defects after exposure to any newer-generation antiepileptic drugs during the first trimester were not statistically different for mothers with epilepsy (adjusted POR, 0.94; 95% CI, 0.65-1.36), mood affective disorder or migraine (adjusted POR, 1.16; 95% CI,

0.28-4.78), or without a diagnosis (adjusted POR, 1.04; 95% CI, 0.53-2.01) ( $P = .94$  for homogeneity).

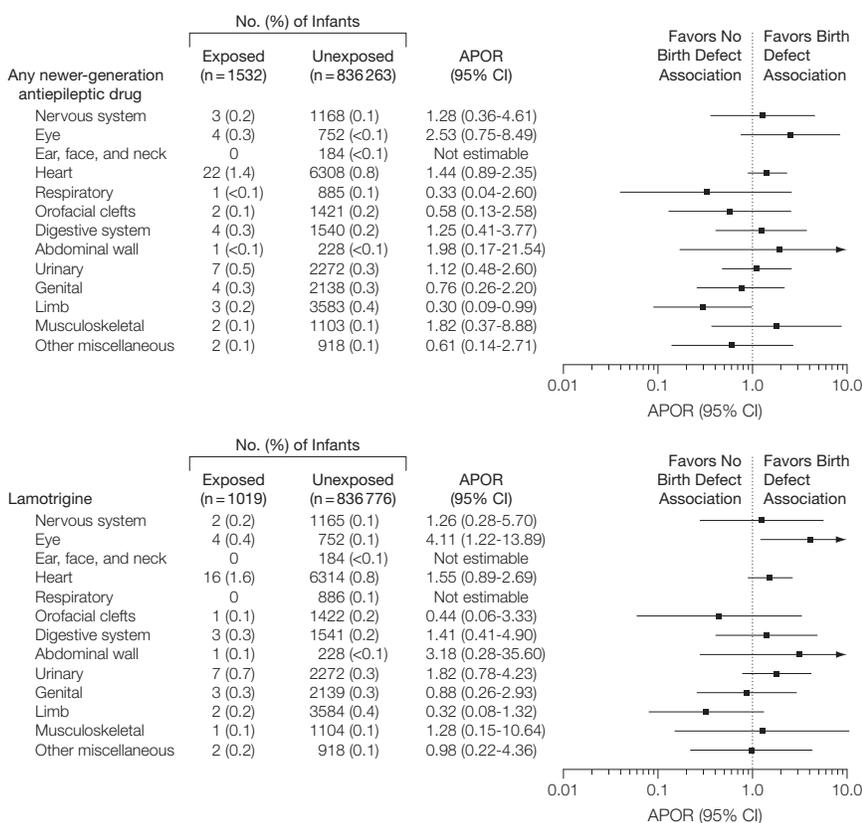
Finally, the temporal trends in the risk of any major birth defects were addressed. The PORs of any major birth defects associated with exposure to any newer-generation antiepileptic drugs were not statistically different during 1996-1998 (adjusted POR, 0.47; 95% CI, 0.15-1.50), 1999-2001 (adjusted POR, 1.18; 95% CI, 0.61-2.26), 2002-2004 (adjusted POR, 1.20; 95% CI, 0.71-2.02), and 2005 through September 2008 (adjusted POR, 0.93; 95% CI, 0.58-1.48) ( $P = .41$  for homogeneity).

**COMMENT**

In a large cohort study of 837 795 pregnancies in Denmark, we found no association between the use of newer-generation antiepileptic drugs during the first trimester and the risk of major birth defects. Unadjusted estimates did show a significant association between exposure to any newer-generation antiepileptic drugs or lamotrigine alone during the first trimester and the risk of major birth defects. Elevated, but not statistically significant, unadjusted PORs also were seen for oxcarbazepine, topiramate, and gabapentin. However, after adjustment for older-generation antiepileptic drug use and epilepsy, no associations remained. It is well established that older-generation antiepileptic drugs are associated with a 2- to 3-fold increased risk of major birth defects.<sup>7</sup> Some of the mothers in the cohort were treated with both older- and newer-generation antiepileptic drugs or switched from older- to newer-generation antiepileptic drugs when pregnancy status was determined, explaining the reduction in risk when adjusting for older-generation antiepileptic drug use.

Maternal diagnosis of epilepsy is associated with use of antiepileptic drugs because the majority of patients with epilepsy receive medical treatment. The possibility that epilepsy itself is associated with an increased risk of birth defects is an ongoing discussion. A meta-analysis showed that untreated

**Figure.** Associations Between First-Trimester Exposures of Newer-Generation Antiepileptic Drugs and Subgroups of Major Birth Defects by Organ System



The adjusted prevalence odds ratios (APORs) were adjusted for maternal use of older-generation antiepileptic drugs during the first trimester and maternal diagnosis of epilepsy before the second trimester. The sum of birth defects from the subgroups is larger than the number of birth defects in the overall analyses in which only the first birth defect was counted because some participants had birth defects from more than 1 subgroup. CI indicates confidence interval.

women with epilepsy were not at an increased risk of having infants with birth defects compared with healthy women.<sup>28</sup> However, the severity of epilepsy and the frequency of seizures in untreated women are unlikely to be comparable with women receiving antiepileptic drug treatment. In our study, maternal epilepsy was associated with a moderately increased risk of birth defects, which explains why maternal epilepsy was a confounder.

Lamotrigine and oxcarbazepine were the antiepileptic drugs most commonly used and our study suggests that an excess risk of 68% is unlikely for any major birth defects for lamotrigine (adjusted POR, 1.18; 95% CI, 0.83-1.68) and 59% for oxcarbazepine (adjusted POR, 0.86; 95% CI, 0.46-1.59). Analyses of topiramate and gabapentin were based on a limited number of exposed cases, but the results indicate that these drugs are not major human teratogens. Risk estimates could not be calculated for levetiracetam due to lack of exposed cases.

In explorative analyses, we found no associations between first-trimester exposure to any antiepileptic drugs and subgroups of major birth defects by organ system. However, a significantly increased risk of eye defects was observed for lamotrigine, but the subgroup only included 4 exposed infants with 4 etiologically different eye defects, which argues against a causal association. Given the explorative nature of the subgroup analyses and the large number of effects estimated, this is likely a chance finding. In general, the subgroup analyses are limited by the number of exposed cases in each subgroup and therefore cannot exclude teratogenic effects with certainty.

Our results are in concert with previous studies of newer-generation antiepileptic drugs. Previous studies using data from the Australian Pregnancy Register of Antiepileptic Drugs and the North American Antiepileptic Drugs and Pregnancy Registry have shown no increased risk of major birth defects after first-trimester exposure to lamotrigine monotherapy compared with

unexposed pregnant women with epilepsy<sup>15</sup> and unexposed pregnant women,<sup>13</sup> respectively. However, in the North American study, the investigators found a strong increased risk of oral clefts. The mean daily dose of lamotrigine was significantly higher for the groups with major birth defects than for those without major birth defects in a registry study from the United Kingdom,<sup>14</sup> but not in a study using the International Lamotrigine Pregnancy Registry.<sup>12</sup> A Finnish nationwide cohort study found no increased risk of birth defects after exposure to oxcarbazepine monotherapy during pregnancy.<sup>16</sup> Other studies from Denmark,<sup>9</sup> Sweden,<sup>3</sup> and the United Kingdom<sup>14,17,18</sup> only report descriptive results, with prevalence of birth defects ranging from 2.0% to 11.2%.

Although the studies using pregnancy registries were comprehensive, they were limited by methodological shortcomings. Enrollment was voluntary and based on referral by health care clinicians or by the women themselves, which may have introduced selection bias. Furthermore, the comparison groups differed, including unexposed pregnant women with epilepsy, pregnant women from another source population, or no control group. The postdelivery follow-up period was usually restricted to birth or 3 months after birth, which meant that malformations diagnosed later were missed. Lastly, loss to follow-up usually ranged from 5% to 26%.

There are some strengths and limitations to our study. The unique registries in Denmark allowed for a nationwide cohort study covering a period of 13 years with independent ascertainment of dispensed prescriptions and birth defects diagnoses, and complete 1-year follow-up of births. Sensitivity analyses with different exposure definitions confirmed the robustness of our results. Birth defect diagnoses were identified through the National Patient Registry with high validity. The predictive value is 88% for birth defects overall<sup>29</sup> and 90% for cardiac malformations<sup>30</sup> in the National Patient

Registry. The overall prevalence of major birth defects was 2.4% in our cohort. This is in accordance with the prevalence found in a study population in Atlanta, Georgia, of 2.17% and 3.15% for defects diagnosed at birth and at any age, respectively,<sup>31</sup> and with EUROCAT data from Europe of 2.04%.<sup>32</sup> However, defects diagnosed in the primary care setting were not included. We expect that number was small because most major birth defects are diagnosed during follow-up in the hospital or in an ambulatory care setting, and infants in our study were followed up for 1 year.

Information on filled prescriptions was obtained through a nationwide prescription drug registry, which eliminates recall bias and increases the completeness and accuracy of drug exposure compared with self-reported use. However, when using filled prescriptions as a proxy for exposure, noncompliance may have overestimated exposure, which will bias the results toward no effect. In addition, women filling anti-epileptic drug prescriptions for epilepsy and bipolar disorder are unlikely to stop taking their medication when pregnancy status is determined because of the risk that seizures pose to the mother and the fetus and the risk of depression. Whether pregnant women with migraine or neuropathic pain will stop taking their medication will depend on the severity of the disorders.

We included a large number of possible confounders, but ascertainment of maternal morbidities may be incomplete because the National Patient Registry does not include diagnostic information from the primary care setting. Furthermore, our study did not include information on abortions. This will bias an association between antiepileptic drug use during pregnancy and a birth defect toward the null if the birth defect itself increases the risk of induced or spontaneous abortion. Lastly, our classification of birth defect subgroups by organ system in the explorative analyses was crude and contained many pathogenetically differ-

ent birth defects within each subgroup. Most teratogens cause specific birth defects and therefore we cannot exclude teratogenic effects with certainty based on the explorative analyses of subgroups by organ system. Further studies investigating newer-generation antiepileptic drugs and the risk of specific birth defects are needed and require larger sample sizes.

Our study, to our knowledge, is the largest analytic cohort study on this topic and provides comprehensive safety information on a class of drugs commonly used during pregnancy. The use of lamotrigine and oxcarbazepine during the first trimester was not associated with moderate or greater risks of major birth defects like the older-generation antiepileptic drugs, but our study cannot exclude a minor excess in risk of major birth defects or risks of specific birth defects. Topiramate, gabapentin, and levetiracetam do not appear to be major teratogens, but our study cannot exclude minor to moderate risks of major birth defects.

**Author Contributions:** Ms Mølgaard-Nielsen and Dr Hviid had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Mølgaard-Nielsen, Hviid.  
**Acquisition of data:** Mølgaard-Nielsen, Hviid.  
**Analysis and interpretation of data:** Mølgaard-Nielsen, Hviid.

**Drafting of the manuscript:** Mølgaard-Nielsen.  
**Critical revision of the manuscript for important intellectual content:** Hviid.

**Statistical analysis:** Mølgaard-Nielsen, Hviid.  
**Obtained funding:** Mølgaard-Nielsen, Hviid.  
**Study supervision:** Hviid.

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**Online-Only Material:** The eMethods, eResults, and eTable 1 and eTable 2 are available at <http://www.jama.com>.

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