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Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations?

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ABSTRACT

Objective: To investigate whether first trimester exposure to lamotrigine (LTG) monotherapy is specifically associated with an increased risk of orofacial clefts (OCs) relative to other malformations, in response to a signal regarding increased OC risk.

Methods: Population-based case-control study with malformed controls based on EUROCAT congenital anomaly registers. The study population covered 3.9 million births from 19 registries 1995–2005. Registrations included congenital anomaly among livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. Cases were 5,511 nonsyndromic OC registrations, of whom 4,571 were isolated, 1,969 were cleft palate (CP), and 1,532 were isolated CP. Controls were 80,052 nonchromosomal, non-OC registrations. We compared first trimester LTG and antiepileptic drug (AED) use vs nonepileptic non-AED use, for mono and polytherapy, adjusting for maternal age. An additional exploratory analysis compared the observed and expected distribution of malformation types associated with LTG use.

Results: There were 72 LTG exposed (40 mono- and 32 polytherapy) registrations. The ORs for LTG monotherapy vs no AED use were 0.67 (95% CI 0.10–2.34) for OC relative to other malformations, 0.80 (95% CI 0.11–2.85) for isolated OC, 0.79 (95% CI 0.03–4.35) for CP, and 1.01 (95% CI 0.03–5.57) for isolated CP. ORs for any AED use vs no AED use were 1.43 (95% CI 1.03–1.93) for OC, 1.21 (95% CI 0.82–1.72) for isolated OC, 2.37 (95% CI 1.54–3.43) for CP, and 1.86 (95% CI 1.07–2.94) for isolated CP. The distribution of other nonchromosomal malformation types with LTG exposure was similar to non-AED exposed.

Conclusion: We find no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine (LTG) monotherapy. Our study is not designed to assess whether there is a generalized increased risk of malformations with LTG exposure.
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GLOSSARY

AED = antiepileptic drug; **ATC** = Anatomic Therapeutic Chemical; **CP** = cleft palate; **FDA** = Food and Drug Administration; **LTG** = lamotrigine; **OC** = orofacial cleft.

Postmarketing surveillance of the second generation antiepileptic drug (AED) lamotrigine (LTG) during pregnancy has recently generated a signal regarding higher risk of orofacial clefts (OCs) based on data from the North American AED Pregnancy Registry. They reported an unexpectedly high prevalence of isolated nonsyndromic, orofacial clefts in infants exposed to LTG monotherapy during the first trimester of pregnancy: 3 isolated cleft palate (CP) and 2 isolated cleft lip with or without palate were identified among 564 exposed pregnancy outcomes, a rate of 8.9 per 1,000.[1] These results were followed by a Food and Drug Administra-

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tion (FDA) alert.[2] Three other registries have reported one or two cases of OC,[3-6] and one none,[7] but have not provided enough evidence to confirm or refute the OC signal.

Case-control studies are recommended to test signals emanating from pregnancy registers.[8] The EUROCAT network of population-based congenital anomaly registers covers more than one quarter of births in Europe, following standardized methodology and contributing to a central database.[9-10] We report a case-control study, with malformed controls, to assess whether first trimester exposure to LTG monotherapy vs nonepileptic non-AED use is specifically associated with an increased risk of OC relative to other malformations. We also report an exploratory analysis of the types of malformations associated with LTG exposure, comparing them to what would be expected in a nonepileptic non-AED exposed population.

METHOD Study population and database. The EUROCAT central database holds individual standardized records of congenital anomaly registrations since 1980 including livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. The standard data on each registration are described in EUROCAT Guide 1.3.[10] One syndrome and up to eight malformations are coded by ICD9 or ICD10 codes. Babies with only anomalies on the EUROCAT list of minor anomalies[10] are excluded. Other variables include date of birth, pregnancy outcome (live, still, termination), maternal age, maternal disease before and during pregnancy (ICD coded + text), and drugs taken in the first trimester of pregnancy. Up to 2004 (birth year), registries could give up to three drug codes (grouped into 20 categories) as well as text information on the drug.[11] From 2005, and for some registries before 2005, drugs are coded according to the Anatomic Therapeutic Chemical (ATC) classification.[12] Information about maternal drug exposure is mainly obtained from obstetric records, and some registries also use maternal interviews after birth or linkage with pharmacy databases.[11]

Criteria for registries to participate in the study were as follows:

1. Maternal epilepsy or antiepileptic drug exposure recorded for at least 3 per 1,000 registrations for the study period. This criterion was set a priori based on population information on epilepsy prevalence to exclude registries with low ascertainment of epilepsy.

2. Specific drug name or complete seven-digit ATC code available for at least 80% of AED exposed babies/fetus for the study period.

Nineteen registries met these criteria. The study period for each registry (table 1) started in or after the year of LTG licensing in the country. The study population comprised a total of 3,881,592 births. The total number of congenital anomaly registrations in the study population was 98,075, of which 11,784 were chromosomal and 86,291 nonchromosomal.

Part I: Case-control study. ***Study design.*** Population-based case-control study, with malformed controls. Odds of LTG exposure among OC registrations (cases) was compared with the odds of LTG exposure among malformed non-OC registrations (controls).

Case definition. Livebirths, fetal deaths from 20 weeks, and terminations of pregnancy following prenatal diagnosis with nonchromosomal OCs. The primary hypothesis concerned isolated OC, the subject of the FDA alert,[2] and secondary hypotheses concerned isolated CP, which carried a higher relative risk than cleft lip in the original signal,[1] and a wider definition of nonsyndromic OC and CP, including multiply malformed cases.

Monogenic syndromes (n = 163) were excluded. Also excluded were cases where OC was secondary to another primary anomaly (n = 345) such as holoprosencephaly or Pierre Robin sequence. Isolated (I) OCs were designated by a panel of three medical geneticists, blind to exposure status, to include only those OCs without another anomaly, or with only a minor or unspecified anomaly,[10] or an anomaly forming part of the OC malformation.

Control definition. Livebirths, fetal deaths from 20 weeks gestation, and terminations of pregnancy following prenatal diagnosis, with nonchromosomal, non OC, major defects.

Exposure definition. Registrations with coded maternal epilepsy or AED exposure (whether for epilepsy or not) were extracted from the database, and verified with participating registries. Exposures were classified as monotherapy vs polytherapy (use of two or more drugs in the first trimester), and by type of AED (lamotrigine, valproic acid, carbamazepine, other). After verification with registries, 98.9% of AED exposures were of known drug name. To avoid misclassification we excluded epileptic mothers without recorded AED exposure from both cases and controls (9 cases, 185 controls). An additional 5 case and 21 control mothers were excluded (mothers with childhood epilepsy or epilepsy prior to pregnancy or unconfirmed epilepsy without AED use).

Statistical analysis. Crude ORs were calculated ignoring the registry of origin. In order to analyze the data taking into account the registry and including all registries (even if they had no exposure to LTG in either cases or controls) the WinBUGS computer package was used to fit multinomial responses with a logistic link. Maternal age was treated as a categorical variable (<20, 20–24, 25–30, 30–35, and 35+ years of age). Due to the small numbers of exposures to LTG it was not possible to adjust simultaneously for both registry and maternal age. ORs are equivalent to a relative risk where the outcome is rare.

Statistical power. We designed the study to answer the concern raised by the FDA alert[1,2] regarding an observed relative risk of isolated OCs of approximately 17 relative to a generally raised risk of other malformations. We estimated with the EUROCAT population expected to be available for study, and the estimated exposure rate, 80% power and $p = 0.05$, that the study could detect an OR of 5 for isolated OCs and 10 for isolated CP, i.e., enough power to confirm or refute an excess of the size of the original signal. The final study population was larger than estimated, giving a higher power.

Part II: Exploratory hypothesis-generating analysis. An exploratory hypothesis-generating analysis compared the proportion of different malformation subgroups, according to EUROCAT subgroup definitions,[10] among all nonchromosomal registrations, between LTG exposed (all and mono) and AED unexposed registrations. Exclusions were the same as for the case-control analysis.

A further analysis compared the proportion of chromosomal registrations among LTG exposed and AED unexposed registrations, controlling for maternal age in 5-year age groups. Assuming no relationship between exposure and chromosomal anomaly

Table 1 Participating registries, study years, number of births surveyed, number and prevalence of orofacial clefts (OC), and number of controls

Registry	Years	Total births	Orofacial cleft cases		Controls, n†
			No.	Prevalence*	
Antwerp, Belgium	1997-2005	162,545	246	1.51	3,491
Basque Country, Spain	1995-2005	193,037	137	0.71	2,576
Cork & Kerry, Ireland	1996-2003	63,007	73	1.16	1,262
Emilia Romagna, Italy	2000-2004	140,726	108	0.77	2,054
Hainaut, Belgium	1997-2005	110,557	153	1.38	2,354
Mainz, Germany	1996-2004	29,859	61	2.04	1,220
Malta	1996-2004	38,495	58	1.51	1,180
Northern Netherlands	1995-2005	216,940	377	1.74	3,921
Norway	1999-2005	406,805	728	1.79	13,440
Odense, Denmark	1995-2004	55,677	104	1.87	1,063
Paris, France	1997-2005	347,778	381	1.10	9,192
Poland	1999-2004	1,189,902	1,744	1.47	15,739
Saxony Anhalt, Germany	1996-2005	146,511	303	2.07	4,115
Strasbourg, France	1997-2002	80,919	117	1.45	2,053
Tuscany, Italy	2002-2005	112,684	107	0.94	1,891
Vaud, Switzerland	1997-2005	65,339	69	1.06	2,070
Wales, UK	1998-2005	255,077	360	1.41	7,872
Wielkopolska, Poland	1999-2004	206,481	320	1.55	3,780
Zagreb, Croatia	1995-2004	59,253	65	1.10	779
Total	1995-2005	3,881,592	5,511	1.42	80,052

*Prevalence of OC per 1,000 births.
†Controls: all nonchromosomal, non-OC registrations.

risk, we would expect a lower proportion of chromosomal registrations if the risk of nonchromosomal anomalies was raised.

Ethics approval. Approved by the University of Ulster Ethics Committee.

RESULTS

Case-control study. A total of 85,563 registrations comprising 5,511 OC cases and 80,052 non-OC controls were eligible for the case-control analysis (table 1). Of the 5,511 OC cases, 4,571 were isolated, and 1,969 had CP of whom 1,532 were isolated.

There were 495 AED exposed cases and controls (table 2) or 5.8 per 1,000 registrations. Seventeen out of 495 had no recorded maternal epilepsy, of whom 1 was exposed to LTG. Over 80%, 409 out of 495, of these AED exposed mothers used monotherapy (table 2). There were 72 LTG exposed cases and controls of which 56% (40/72) were LTG monotherapy (table 2). The proportion of AED exposed registrations declined over time (table 3) while the proportion of LTG exposure per 1,000 registrations doubled from 0.5 in 1995–1998 to 1.1 in the period 2002–2005 (table 3). The proportion of LTG use among all AED use grew from 7.3% (6/82) in 1995–1998 to 20.5% (45/219) in the period 2002–2005 (table 3).

Table 2 Antiepileptic drug (AED) exposure among registrations*

	No.	Per 1,000 registrations (n = 85,563)
Any AED	495	5.79
Any AED monotherapy	409	4.78
Valproic acid monotherapy	181	2.12
Carbamazepine monotherapy	125	1.46
Lamotrigine monotherapy	40	0.47
Other monotherapy†	63	0.74
Any AED polytherapy	86	1.01
Including valproic acid	57	0.67
Including carbamazepine	39	0.46
Including lamotrigine‡	32	0.37
Other polytherapy§	4	0.05

*Registrations include cases of orofacial cleft and controls (other malformations) as defined in Methods.
†Twenty-six phenobarbital, 9 oxcarbazepine, 7 clonazepam, 5 phenytoin, 3 primidone, 3 topiramate, 2 methylphenobarbital, 1 levetriacetam, 1 ethosuximide, 6 unspecified.
‡Twenty-two out of 32 of lamotrigine polytherapy included valproic acid and 8 out of 32 included carbamazepine.
§Polytherapy without valproic acid, carbamazepine, or lamotrigine.

Table 3 Year of birth of registrations* by case and exposure status

		Cases						Exposure					
		Orofacial cleft			Cleft palate			Any AED			Lamotrigine		
Year of birth	Reg, n	I	M	I+M per 1,000 Reg	I	M	I+M per 1,000 Reg	Mono	Poly	Any AED per 1,000 Reg	Mono	Poly	Any LTG per 1,000 Reg
1995–1998	11,582	542	109	56.2	156	40	16.9	70	12	7.1	2	4	0.5
1999–2001	30,952	1,748	367	68.3	577	179	24.4	166	28	6.3	10	11	0.7
2002–2005	43,029	2,281	464	63.8	799	218	23.6	173	46	5.1	28	17	1.1

*Registrations (Reg) include cases of orofacial cleft and controls (other malformations) as defined in Methods.
I = isolated; M = multiply malformed; AED = antiepileptic drug; Mono = monotherapy; Poly = polytherapy; LTG = lamotrigine.

AED exposed registrations were similar in maternal age to nonexposed (28.8 vs 28.9 years), but LTG exposed tended to be younger: 26.8 years for monotherapy and 27.8 for polytherapy. OC cases had a similar mean maternal age to controls, but more detailed analysis shows a slightly higher risk of OC in young mothers.[13]

As expected given the types of anomalies, there were more terminations of pregnancy following prenatal diagnosis among controls (5,718/80,052 or 7.1%) than among OC cases (159/5,511 or 2.9%). The proportion of fetal deaths was similar between controls (1.3%) and cases (1.4%). The proportion of AED exposure was 5.6 per 1,000 registrations among livebirths, 8.6 per 1,000 among fetal deaths, and 8.3 per 1,000 among terminations.

Table 4 shows the ORs for OC (in four categories) with AED mono and polytherapy, and LTG mono and polytherapy vs no AED exposure. Adjusting for registry did not materially affect the ORs (data not shown); however, adjusting for maternal age did reduce the ORs for LTG mono and polytherapy as younger mothers were more likely to take LTG and they were also at a slightly increased risk of OCs. Therefore for consistency all crude ORs and maternal age-adjusted ORs are presented. There was no evidence of an increased risk of isolated OC relative to other malformations with LTG monotherapy vs no AED exposure (table 4, OR = 0.80, 95% CI 0.11–2.85). Nor was there an increased risk for any of the other three categories of OC (table 4).

Significantly increased ORs were found with any AED exposure vs no AED exposure for OC (adjOR = 1.43, 95% CI 1.03–1.93), CP (adjOR = 2.37, 95% CI 1.54–3.43), and isolated CP (adjOR = 1.86, 95% CI 1.07–2.94) (table 4). ORs for any AED therapy were higher for mono than for polytherapy, higher for CP than all OCs, and higher for isolated and multiple OCs combined than isolated OCs alone (table 4). However, due to the small sample sizes, none of these differences were significant.

Exploratory analyses. Table 5 gives the distribution of nonchromosomal malformation subgroups among the 72 LTG exposed and 40 LTG monotherapy exposed cases and controls, compared to non-AED exposed. Shown in table 5 are all EUROCAT subgroups with at least one LTG exposed registration. Cardiac anomalies are the most frequent anomalies, irrespective of exposure (31.0% of non-AED exposed registrations and 31.9% of exposed registrations). Most subgroups had only one or two registrations associated with LTG exposure, so a comparison of proportions with non-AED exposed registrations is imprecise. Moreover, with 37 subgroups, approximately two would be expected by chance alone to show a difference with a probability of less than 1 in 20. In this context, we found one significant observation related to LTG monotherapy: 5 cases of clubfoot (without spina bifida) where 1.7 would be expected ($p < 0.05$). In the LTG group including mono and polytherapy three significant differences were found: spina bifida was in excess ($p < 0.01$) as well as cystic kidney ($p < 0.05$) and clubfoot ($p < 0.05$).

The proportion of chromosomal registrations (n = 11,781) among all non-AED exposed registrations (chromosomal + nonchromosomal) was 12.0% compared with 4.0% for all LTG exposed (n = 3), and 4.8% for LTG monotherapy (n = 2). The relative odds of a nonchromosomal case rather than a chromosomal case given LTG monotherapy was 2.86 (95% CI 1.00–12.5), adjusted for maternal age.

DISCUSSION We found no evidence of an increased risk of isolated OC relative to other nonchromosomal malformations for LTG monotherapy exposure (adjOR = 0.80, 95% CI 0.11–2.85), nor any evidence of an increased risk for isolated CP (adjOR = 1.01, 95% CI 0.03–5.57). Despite the huge size of our study population, LTG exposure and OCs are both so rare that the CIs around our estimates of risk are wide. We can at present consider very unlikely a more than threefold risk of isolated OCs relative to other nonchromosomal malformations. Our results therefore do not

Table 4 Orofacial cleft (OC) ORs for antiepileptic drug (AED) and lamotrigine exposure compared to no AED exposure

	Isolated OC (n = 4,571)	Isolated & mult. OC (n = 5,511)	Isolated CP (n = 1,532)	Isolated & mult. CP (n = 1,969)
No AED	4,540	5,467	1,516	1,943
Reference	1.0	1.0	1.0	1.0
Any AED				
No.	31	44	16	26
OR	1.21 (0.81–1.74)	1.42 (1.02–1.94)	1.86 (1.05–3.07)	2.36 (1.52–3.52)
$OR_{adjusted}$	1.21 (0.82–1.72)	1.43 (1.03–1.93)	1.86 (1.07–2.94)	2.37 (1.54–3.43)
Any AED monotherapy				
No.	26	37	15	23
OR	1.23 (0.79–1.83)	1.45 (1.00–2.04)	2.12 (1.17–3.55)	2.53 (1.58–3.87)
$OR_{adjusted}$	1.23 (0.81–1.79)	1.46 (1.02–2.02)	2.11 (1.20–3.42)	2.55(1.61–3.77)
Any AED polytherapy				
No.	5	7	1	3
OR	1.11 (0.35–2.70)	1.29 (0.50–2.79)	0.66 (0.02–3.82)	1.56 (0.31–4.72)
$OR_{adjusted}$	1.04 (0.37–2.40)	1.24 (0.51–2.57)	0.48 (0.02–2.58)	1.41 (0.32–3.94)
Lamotrigine monotherapy				
No.	2	2	1	1
OR	0.92 (0.11–3.57)	0.77 (0.09–2.97)	1.38 (0.03–8.19)	1.08 (0.03–6.39)
$OR_{adjusted}$	0.80 (0.11–2.85)	0.67 (0.10–2.34)	1.01 (0.03–5.57)	0.79 (0.03–4.35)
Lamotrigine polytherapy				
No.	2	3	0	1
OR	1.21 (0.14–4.78)	1.51 (0.29–4.86)	0.00 (0.00–6.96)	1.41 (0.03–8.53)
$OR_{adjusted}$	1.00 (0.14–3.60)	1.34 (0.29–3.95)	—	1.02 (0.03–5.61)

mult. = multiply malformed; CP = cleft palate; $OR_{adjusted}$ = adjusted for maternal age.

support the results of the North American AED Pregnancy Register suggesting a 14-fold increased risk of isolated OCs[1,2(revised in 6)] against a 1.4-fold increase in non-OC malformations, i.e., a 10-fold increased risk of isolated OCs relative to other malformations. We find a twofold higher rate of isolated OCs in Europe (1.2 per 1,000 births), with some variation between countries,[14,15] than in the single hospital comparison population used by the North American AED Pregnancy Registry (0.37 per 1,000[1] revised to 0.6 per 1,000[6]), demonstrating the importance of analyzing comparable exposed and unexposed populations. Given the concern about very high relative risks of OCs with LTG monotherapy, we report here the results to date, but continued surveillance will allow us to address the possibility of less than threefold relative risks more precisely.

Our case-control study is not designed to assess whether there is a generalized increased risk of malformations with LTG exposure, for which we would need to collect information on non-malformed controls as a comparison group, an area EUROCAT intends to develop in the future. It is possible therefore that some malformations resulting from LTG exposure were in our control group, and moreover that OC risk, while not raised relative to other malformations, is raised to the same degree as malformations in general. Our exploratory analyses showed that 1) there is no malformation subgroup that stands out as of particular concern in relation to monotherapy, suggesting that any excess risk, if present, is very nonspecific, and 2) nonchromosomal anomalies are overrepresented among LTG-exposed registrations compared to chromosomal, compatible with a generally raised risk of nonchromosomal malformations but based on very small numbers. The evidence from other studies about general malformation risk is inconclusive. To date, publications have reported 2,665 monotherapy exposed pregnancy outcomes,[1,4,6,7,16] although some of these may come from overlapping pregnancy registers. The UK register with 647 LTG monotherapy exposed fetuses found a general malformation rate of 3.2% (95% CI 2.1–4.9) excluding genetic syndromes. The rate of major malformations among the carbamazepine exposed, the main available comparison group, was 2.2% (95% CI 1.4–3.4).[4] The GSK International Lam-

Table 5 Distribution* of malformation subgroups by lamotrigine exposure

Nonchromosomal anomaly subgroup	Non-AED exposed		Lamotrigine exposed			
	85,068 registrations†		72 mono or polytherapy exposed registrations		40 monotherapy exposed registrations	
	No.	Proportion, %	No.	Proportion, %	No.	Proportion, %
Nervous system	7,948	9.3	12	16.7	5	12.5
Neural tube defects	3,582	4.2	6	8.3	2	5.0
Spina bifida	1,930	2.3	6	8.3	2	5.0
Hydrocephaly	1,952	2.3	1	1.4	0	—
Microcephaly	730	0.9	2	2.8	1	2.5
Eye	1,379	1.6	2	2.8	1	2.5
Ear, face, & neck	1,119	1.3	3	4.2	1	2.5
Congenital heart disease	26,347	31.0	23	31.9	12	30.0
Common arterial truncus	258	0.3	1	1.4	0	—
Ventricular septal defect	11,872	14.0	8	11.1	2	5.0
Atrial septal defect	8,402	9.9	10	13.9	5	12.5
Atrial ventricular septal defect	639	0.8	2	2.8	1	2.5
Tetralogy of Fallot	986	1.2	1	1.4	1	2.5
Pulmonary valve stenosis	1,362	1.6	1	1.4	1	2.5
Respiratory	1,675	2.0	3	4.2	1	2.5
Orofacial clefts‡	5,467	6.4	5	6.9	2	5.0
Cleft lip	3,524	4.1	3	4.2	1	2.5
Cleft palate	1,943	2.3	2	2.8	1	2.5
Digestive system	5,382	6.3	7	9.7	5	12.5
Esophageal atresia	899	1.1	2	2.8	1	2.5
Atresia/stenosis small intestine	299	0.3	1	1.4	1	2.5
Anorectal	1,073	1.3	2	2.8	2	5.0
Diaphragmatic hernia	761	0.9	2	2.8	1	2.5
Urinary	11,093	13.0	11	15.3	4	10.0
Cystic kidney	2,009	2.4	5	6.9	0	—
Cong. hydronephrosis	3,806	4.5	1	1.4	1	2.5
Genital	6,916	8.1	5	6.9	3	7.5
Hypospadias	5,408	6.4	4	5.6	2	5.0
Limb	16,407	19.3	19	26.4	11	27.5
Limb reduction	2,202	2.6	1	1.4	0	—
Upper limb reduction	1,596	1.9	1	1.4	0	—
Clubfoot	3,733	4.4	7	9.7	5	12.5
Hip dislocation	2,941	3.5	1	1.4	0	—
Polydactyly	3,568	4.2	5	6.9	2	5.0
Syndactyly	2,181	2.6	1	1.4	0	—
Musculoskeletal	3,052	3.6	4	5.6	3	7.5
Disorders of skin	1,490	1.8	3	4.2	1	2.5

*One baby can be counted in more than one subgroup if he or she has multiple malformations, but only once in the total.
†The total number of registrations (85,563) minus those exposed to AEDs (495).
‡Secondary clefts excluded (of whom none were exposed to lamotrigine); see Methods.
AED = antiepileptic drug.

otrigine pregnancy register with 1,053 first trimester LTG exposed fetuses found a prevalence of major congenital anomalies of 2.6% (95% CI 1.7–3.8%)[6] excluding genetic syndromes, without a direct comparison group, and possibly biased by a high 26.6% loss to follow-up rate. The North American AED

Pregnancy Registry has reported 15 infants with major malformations among 564 LTG monotherapy exposed fetuses, a rate of 2.7% (95% CI 1.5–4.3), which they compare to an unexposed comparison group rate of 1.6%, giving a relative risk of 1.7 (95% CI 1.0–2.7),[1] or 1.4 excluding OC. The Australian Pregnancy register reported 6 malformed babies among 102 LTG monotherapies (5.9%), similar to the rate for carbamazepine (10/198 or 5.0%).[16] The Swedish Medical Birth Registry reported 14 malformed children, including minor malformations but not including terminations of pregnancy for fetal anomaly, among 347 women using LTG monotherapy, a rate of 4.0% (95% CI 2.3–6.8),[6] compared to a malformation rate of 3.6% in the general population. In Denmark, one case of VSD with lamotrigine polytherapy[7] was reported among 51 LTG exposed fetuses (proportion monotherapy not specified).

We did not have information on lamotrigine dose. We cannot therefore exclude the possibility of a specific risk of OCs associated with high dosage LTG therapy, although if high dosage therapy were common this would have been detectable in the overall result. A higher mean dose among malformed compared to non-malformed outcomes has been found in the United Kingdom[4] and Australia,[16] although the latter was not significant, but the GSK International Lamotrigine Registry could not find evidence of a dose-response effect.[3] It is possible that lamotrigine dosages have been increasing in response to findings regarding kinetics during pregnancy,[17] and further surveillance of this issue is necessary.

We found an increased risk of OC relative to other nonchromosomal malformations for AED exposure in general, which is consistent with much of the literature on drugs such as valproic acid and carbamazepine commonly used by epileptic mothers in our study population.[4,18-20] It is of interest that the increase in risk of CP with AED exposure is higher than that of cleft lip (though not significantly). In our European population, there was a 2.5-fold increase of CP (isolated and multiple combined) relative to other malformations with AED monotherapy. The increase in risk for multiple malformations including OC is higher than the increase in risk for isolated OC (though again not significantly). We suggest that in the future, attention should not be focused only on isolated OCs, but also on multiply malformed individuals with OCs. The tendency for strong teratogens to produce multiple malformations is well established.[21] We also find higher risks of OCs with monotherapy than with polytherapy. This may in part reflect the increased risk of other malformations than OC rather than the decreased risk of OC, with polytherapy.

The main strengths of our study were its huge geographically defined study population, and the well validated, comparable, and specific information about congenital anomaly diagnoses in exposed and unexposed pregnancies. The overall rate of AED exposure—5.8 per 1,000 registrations—is higher than estimated in the general pregnant population (for example, Dutch first trimester AED exposure is 2.5 per 1,000[22]), consistent with a higher risk of malformation with AED exposure, and confirms good ascertainment of AED exposure. The validity of our data for the detection of AED-associated risks of specific malformations is further supported by finding the well known strong association between valproic acid and spina bifida in an embedded validation study (appendix 2), and the commonly documented association of OC with other AED.

Postmarketing surveillance of the teratogenic effects of AED exposure is essential to provide women and clinicians with the safety information they need to make optimal decisions. Very large population sizes are needed for surveillance as both AED exposure and congenital anomalies are rare. We have demonstrated here the usefulness of a multicentric case-control approach based on congenital anomaly registers for addressing signals relating to specific malformations emanating from pregnancy cohorts.

Our study does not support the very large specific risk of OCs reported by one previous study (see Note Added in Proof). Further surveillance is recommended to rule out smaller relative risks (less than threefold) of OCs, to investigate whether other malformation groups are at excess risk, and to investigate risks associated with high dose exposure.

NOTE ADDED IN PROOF

The full publication of the North American AED Registry study was online April 30, 2008,[23] after acceptance of our paper for publication. The final figures in this publication differ from those we quoted from previous publications[1,2,6]; the rate of isolated OCs among LTG monotherapy-exposed pregnancies was revised to 7.3/1,000, and the rate in the comparison group to 0.7/1,000, resulting in an increased risk of 10.4 (95% CI 4.3–24.9).

AUTHOR CONTRIBUTIONS

H.D. and L.J.v.B. drafted the protocol and paper. L.J.v.B., J.J., and M.L. coordinated the study. J.J. conducted the literature review. M.L. and J.J. compiled the study database. J.J. conducted validation and coding of drug exposure information. J.J. constructed the tables. J.M. (Chartered Statistician, The Royal Statistical Society) conducted the statistical analysis. M.L., J.J., and J.M. corrected all versions of the paper. Among the EUROCAT Antiepileptic Drug Exposure Working Group: E.C., D.W., and I.B. classified cleft cases; C.D.V., E.G., M.B., and H.d.W. reviewed the protocol. E.G., M.B., E.C., I.B., C.D.V., and all other members not mentioned above contributed data to the study from their registry, checked and are responsible for the accuracy of drug exposure information, checked data tables, and commented on the first and final paper drafts.

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APPENDIX 1

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APPENDIX 2

A validation study was also conducted to determine whether the well-known association between valproic acid and spina bifida (Omtzigt 1992[24]) could be detected in the EUROCAT data, since this was our first full AED study. The same dataset was used, with the same exclusions as described for Part I, but the exposure of interest was valproic acid monotherapy vs no AED use and cases were nonchromosomal spina bifida registrations, controls were non–spina bifida, nonchromosomal registrations. There were 1,979 nonchromosomal spina bifida registrations, of which 23 were valproic acid monotherapy exposed and 1,933 were not exposed to any AED. Of 83,801 non–spina bifida, nonchromosomal registrations, 158 were valproic acid monotherapy exposed and 83,643 were not exposed to any AED. Comparing VPA exposure to no AED exposure, the crude OR was 6.3 (95% CI 4.1–9.8). Adjusting for age made no material difference.

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