Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs

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Abstract

Objective

To assess the association between exposure to monotherapy with 10 different antiepileptic drugs (AEDs) during the first 2 months of pregnancy and the risk of 23 major congenital malformations (MCMs).

Methods

This nationwide cohort study, based on the French health care databases, included all pregnancies ≥20 weeks and ending between January 2011 and March 2015. Women were considered to be exposed when an AED had been dispensed between 1 month before and 2 months after the beginning of pregnancy. The reference group included pregnant women with no reimbursement for AEDs. MCMs were detected up to 12 months after birth (24 months for microcephaly, hypospadias, and epispadias). Odds ratios (ORs) were adjusted for potential confounders for MCMs with at least 5 cases. Otherwise, we calculated crude ORs with exact confidence intervals (CIs).

Results

The cohort included 1,886,825 pregnancies, 2,997 of which were exposed to lamotrigine, 1,671 to pregabalin, 980 to clonazepam, 913 to valproic acid, 579 to levetiracetam, 517 to topiramate, 512 to carbamazepine, 365 to gabapentin, 139 to oxcarbazepine, and 80 to phenobarbital. Exposure to valproic acid was associated with 8 specific types of MCMs (e.g., spina bifida, OR 19.4, 95% CI 8.6–43.5), and exposure to topiramate was associated with an increased risk of cleft lip (6.8, 95% CI 1.4–20.0). We identified 3 other signals. We found no significant association for lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, and gabapentin.

Conclusions

These results confirm the teratogenicity of valproic acid and topiramate. Because of the small numbers of cases and possible confounding, the other 3 signals should be interpreted with appropriate caution.

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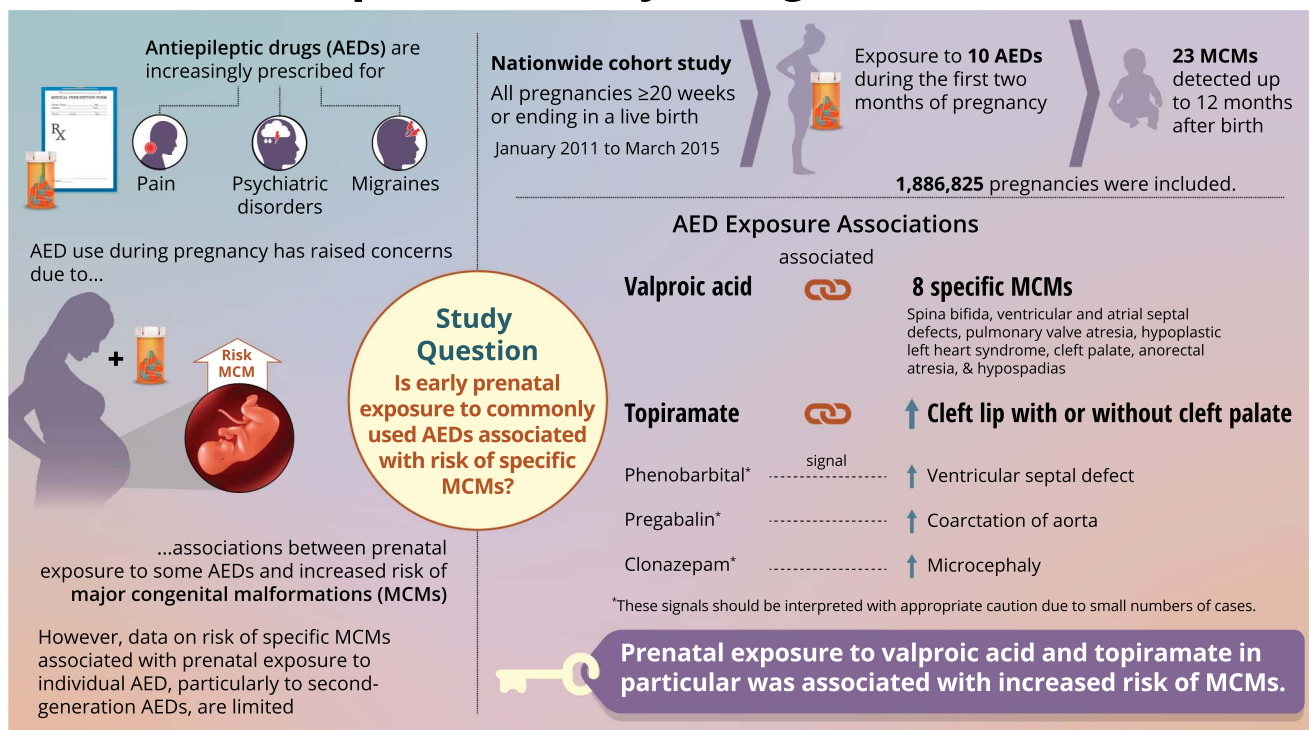
Glossary

AED = antiepileptic drug; **aOR** = adjusted odds ratio; **CI** = confidence interval; **CMU-C** = complementary universal health insurance; **DCIR** = French national health insurance database; **EUROCAT** = European Surveillance of Congenital Anomalies; **ICD-10** = *International Classification of Diseases, 10th revision*; **LTD** = long-term disease; **MCM** = major congenital malformation; **OR** = odds ratio; **PMSI** = French hospital discharge database; **RR** = relative risk.

Prenatal AED Exposure and Major Congenital Malformations

Antiepileptic drugs (AEDs) are increasingly prescribed for
- Pain
- Psychiatric disorders
- Migraines

AED use during pregnancy has raised concerns due to...

Risk MCM

Study Question
Is early prenatal exposure to commonly used AEDs associated with risk of specific MCMs?

...associations between prenatal exposure to some AEDs and increased risk of **major congenital malformations (MCMs)**

However, data on risk of specific MCMs associated with prenatal exposure to individual AED, particularly to second-generation AEDs, are limited

Nationwide cohort study
All pregnancies ≥20 weeks or ending in a live birth
January 2011 to March 2015

Exposure to **10 AEDs** during the first two months of pregnancy → **23 MCMs** detected up to 12 months after birth

1,886,825 pregnancies were included.

AED Exposure Associations

Valproic acid — associated — **8 specific MCMs**
Spina bifida, ventricular and atrial septal defects, pulmonary valve atresia, hypoplastic left heart syndrome, cleft palate, anorectal atresia, & hypospadias

Topiramate — associated — ↑ **Cleft lip with or without cleft palate**

Phenobarbital* — signal — ↑ Ventricular septal defect

Pregabalin* — ↑ Coarctation of aorta

Clonazepam* — ↑ Microcephaly

*These signals should be interpreted with appropriate caution due to small numbers of cases.

Prenatal exposure to valproic acid and topiramate in particular was associated with increased risk of MCMs.

Neurology®

Antiepileptic drugs (AEDs), particularly newer AEDs, are increasingly prescribed for a wide range of medical conditions other than epilepsy such as pain, psychiatric disorders, and migraine.[1] The prevalence of AED use during pregnancy has reached 21.9 per 1,000 pregnancies in the United States[2] across all indications, while it ranges from 4.3 per 1,000 in the Netherlands to 6.0 in Wales[3] and 6.7 in France.[4]

Safety studies on AED use during pregnancy are therefore of paramount importance, especially because prenatal exposure to some AEDs has already been associated with a risk of major congenital malformations (MCMs).[5] The magnitude of this risk is known to be influenced by the type of AED, and the MCMs associated with teratogenic AEDs are limited to specific types of malformations.[6] However, data on the risk of specific MCMs associated with prenatal exposure to individual AEDs, particularly to newer AEDs, are limited because few individual studies have sufficient power to detect excess risks of specific malformations.[5–9]

The French health care databases, covering 99% of the 67 million inhabitants in France,[10] can therefore be useful for conducting such studies on rare drug exposures and rare neonatal outcomes. The objective of this study was to assess the association between prenatal exposure to monotherapy with the most commonly used AEDs during the first 2 months of pregnancy and the risks of 23 specific MCMs using the French health care databases.

Methods

Study design and data sources

We performed this nationwide cohort study using the French National Health Insurance claims information system (Système national d'information interrégimes de l'Assurance maladie), consisting mainly of 2 nationwide datasets linked by a unique patient identifier: the French national health insurance database (DCIR) and the French hospital discharge database (PMSI).[11] The DCIR database contains all

individualized and anonymous health care claims reimbursed by French National Health Insurance. In particular, these claims data include dispensed drugs coded according to the Anatomical Therapeutic Chemical classification and outpatient medical procedures coded according to the French medical classification for clinical procedures. The DCIR database also collects patient data such as age, sex, and eligibility for complementary universal health insurance (CMU-C), which provides free access to health care for low-income people.[12] Eligibility for 100% health insurance coverage for serious and costly long-term diseases (LTDs), coded according to the ICD-10, is also recorded in the DCIR database. The PMSI database provides detailed medical information on all admissions to public and private hospitals in France, including discharge diagnosis ICD-10 codes, medical procedures coded according to the French medical classification for clinical procedures, and data related to pregnancy such as gestational age. In particular, almost all deliveries are recorded in the PMSI database because out-of-hospital delivery is rare in France, accounting for 0.4% of all births in 2005 to 2006.[13]

This linkage has previously been used to conduct large-scale pharmacoepidemiologic studies.[14–16]

Study population

All pregnancies ending between January 2011 and March 2015 with at least 20 weeks of gestation were eligible for inclusion, because pregnancies cannot be linked to neonatal data before 2011 and no birth stay was coded for pregnancies <20 weeks of gestation. If a woman had several pregnancies during the study period, all of them were taken into account. We identified pregnancies on the basis of their outcome from the PMSI database using discharge diagnoses and medical procedures indicative of completion of a pregnancy.[4] The mother had to be enrolled in the national health insurance general scheme for salaried workers, which represents 75% of the French population, during the penultimate year before pregnancy.

We excluded twin pregnancies, which are associated with an increased risk of birth defects,[17] and pregnancies that could not be linked to neonatal data. To avoid any potential differences in the duration of follow-up across exposure groups, resulting in underestimation of the number of MCMs among exposure groups with shorter follow-up, all live children were required not to be lost to follow-up during their first year of life. We also excluded all pregnancies with teratogenic infections (table e-1 available from Dryad, doi.org/10.5061/dryad. qg22n65) or exposure to teratogenic medications (table e-2 available from Dryad) during the first 2 months, as well as pregnancies with a documented chromosomal abnormality identified by hospital discharge diagnoses at birth coded as Q90 to Q99.

Exposure

Women were considered to be exposed when an AED (table e-3 available from Dryad, doi.org/10.5061/dryad.qg22n65)

had been dispensed between 1 month before and 2 months after the beginning of pregnancy; AED prescriptions are dispensed with a 30-day supply. Monotherapy was defined as the absence of any other AED dispensed during the same period. AEDs rarely used in monotherapy during pregnancy (≤10 exposed pregnancies) were not included in this study.

We also calculated a cumulative dose over the first 2 months of pregnancy: the dose of AED dispensed was equally distributed over the 30 days after dispensing, and these daily doses were then added over the first 2 months of pregnancy. The reference group included pregnant women with no reimbursement for AEDs.

Outcomes

Because some MCMs remain unidentified at birth,[18] we detected MCMs up to 12 months (24 months for microcephaly, hypospadias, and epispadias) after birth using hospital discharge diagnoses or specific medical procedures (table 1). These outcomes were selected from the list of MCMs of the European Surveillance of Congenital Anomalies (EUROCAT) network and had to be accurately identifiable in the PMSI database. We finally studied 23 specific MCMs, including some MCMs known to be associated with prenatal exposure to certain AEDs.

We constructed these algorithms in collaboration with a working group composed of experts in malformation coding and compared the frequency of each type of malformation observed in the study population to data from French local registries and the EUROCAT registry. Because anencephaly frequently results in early termination of pregnancy (before 20 weeks of gestation), the number of cases identified in the databases was much lower than the numbers derived from registries. This study therefore does not report the results for anencephaly. Because of imprecise or excess coding, we also do not report the results for dysmorphic facial features and congenital limb malformations other than talipes equinovarus.

Except for the most severe MCMs (spina bifida and bilateral renal agenesis), for which therapeutic abortions and stillbirths were also taken into account, we limited the study population to live births because of incomplete coding of malformations for therapeutic abortions.

Covariates

We identified potential confounding factors. Sociodemographic covariates included maternal age at birth (<25, 25–29, 30–35, and ≥35 years), mother's eligibility for CMU-C, and year of start of pregnancy. We defined preconception folic acid supplementation as at least 1 dispensing between 1 month before pregnancy and 3 months after the start of pregnancy. We identified pregestational diabetes by dispensing of antidiabetic drugs on at least 3 different dates (2 different dates when 3-month packs were dispensed) in the year before pregnancy,[19] excluding dispensing between the sixth month and the end of a potential previous pregnancy to avoid considering gestational diabetes as pregestational diabetes.

Table 1 List of the 23 specific MCMs and related ICD-10 diagnosis codes and/or medical procedures

	ICD-10 diagnosis codes and/or medical procedures
Anomalies of the nervous system	
Spina bifida	Q05
Microcephaly (without craniosynostosis)	Q02 + brain MRI
Cardiac anomalies	
Ventricular septal defect	Q21.0 + echocardiography
Atrial septal defect	Q21.1 + echocardiography
Tetralogy of Fallot	Q21.3 or association of 4 diagnosis codes (Q21.1, Q21.0, Q20.3 and Q22.1) or surgical repair for tetralogy of Fallot
Pulmonary valve atresia	Q22.0 + specific medical procedures
Hypoplastic left heart syndrome	Q23.4
Hypoplastic right heart syndrome	Q22.6
Ebstein anomaly	Q22.5
Discordant ventriculoarterial connection	Q20.3
Coarctation of aorta	Q25.1 + at least 2 echocardiographies
Orofacial clefts	
Cleft lip with or without cleft palate	Q36-Q37
Cleft palate	Q35
Anomalies of the digestive system	
Atresia of esophagus	Q39.0-Q39.1
Anorectal atresia	Q42.0-Q42.3
Genitourinary anomalies	
Hypospadias	Q54 + urethroplasty for hypospadias or urethral meatoplasty
Epispadias	Q64.0 or penis lengthening surgery for epispadias
Bilateral renal agenesis	Q60.1
Other anomalies	
Gastroschisis	Q79.3
Omphalocele	Q79.2
Diaphragmatic hernia	Q79.0
Talipes equinovarus	Q66.0 + specific medical procedures
Craniosynostosis	Q75.0 + specific medical procedures

Abbreviation: ICD-10 = *International Classification of Diseases, 10th revision*; MCM = major congenital malformation.

We also searched the databases for LTD and hospital discharge diagnoses of epilepsy and mood (affective) disorders during the 3 years before pregnancy. All Anatomical Therapeutic Chemical codes, hospital discharge diagnoses, and LTD diagnoses are given in table e-4 (available from Dryad, doi.org/10.5061/dryad.qg22n65).

Statistical analysis

For each AED, we compared baseline covariates between exposed and unexposed pregnancies using the χ^2 test. For each specific MCM, we calculated numbers of events and crude event rates in each AED exposure group and in the reference group. For MCMs with <5 cases per treatment group, we calculated crude odds ratios (ORs) with exact confidence intervals (CIs). For MCMs with at least 5 cases per treatment group, logistic regression models were conducted, and ORs were adjusted (aOR) for maternal age, mother's eligibility for CMU-C, year of start of pregnancy, preconception folic acid supplementation, and pregestational diabetes. Logistic regression models accounted for correlations within women with multiple pregnancies by using generalized estimating equations.

We conducted a sensitivity analysis to account for possible misclassification of exposure at the beginning of pregnancy: a woman was considered to be exposed when an AED had been dispensed at least once during the first 2 months of pregnancy.

Data extraction and statistical analysis were performed with SAS Enterprise Guide 4.3 software (SAS Institute, Inc, Cary, NC).

Standard protocol approvals, registrations, and patient consents

This observational cohort study based on the French health care databases was approved by the French Data Protection Agency (Commission nationale de l'informatique et des libertés) and did not require patient consent or ethics committee approval.

Data availability

Permanent access to the French health care databases is automatically granted to certain government agencies, public institutions, and public service authorities. Temporary access for studies and research is possible on request from the national health data institute (Institut National des Données de Santé).

Results

Of a total of 2,698,787 pregnancies potentially eligible for inclusion, we excluded 441,609 (16.4%) pregnancies that could not be linked to neonatal data, 48,289 (1.8%) twin pregnancies, 311,530 (11.5%) pregnancies for which the child was lost to follow-up, and 10,534 (0.4%) pregnancies with teratogenic infections, exposure to teratogenic medications,

or a documented chromosomal abnormality (figure e-1 available from Dryad, doi.org/10.5061/dryad.qg22n65). The cohort included 1,886,825 pregnancies, representing 69.9% of all eligible pregnancies. Among these pregnancies, 1,870,234 (99.1%) ended in a live birth, 9,848 (0.5%) in a stillbirth, and 6,743 (0.4%) in a therapeutic abortion; 8,794 were exposed to AED monotherapy, 2,997 (34.1%) of which were exposed to lamotrigine, 1,671 (19.0%) to pregabalin, 980 (11.1%) to clonazepam, 913 (10.4%) to valproic acid, 579 (6.6%) to levetiracetam, 517 (5.9%) to topiramate, 512 (5.8%) to carbamazepine, 365 (4.2%) to gabapentin, 139 (1.6%) to oxcarbazepine, 80 (0.9%) to phenobarbital (table 2), and 41 (0.5%) to another AED monotherapy.

Women exposed to AEDs, except for levetiracetam, were older than unexposed women. They more frequently had low incomes, except for women exposed to lamotrigine and topiramate, and were more commonly reimbursed for folic acid, except for women exposed to clonazepam and pregabalin. Pregestational diabetes was more frequent among women exposed to AEDs, except for women exposed to oxcarbazepine and valproic acid. Few women were hospitalized or had an LTD for epilepsy among those exposed to pregabalin, clonazepam, and gabapentin (table 2).

Exposure to valproic acid was associated with increased risks of spina bifida (aOR 19.4, 95% CI 8.6–43.5), ventricular (aOR 4.0, 95% CI 2.1–7.8) and atrial (aOR 9.0, 95% CI 5.4–15.0) septal defects, pulmonary valve atresia (OR 27.8, 95% CI 3.3–102.5), hypoplastic left heart syndrome (OR 19.6, 95% CI 2.4–71.7), cleft palate (OR 5.4, 95% CI 1.1–15.8), anorectal atresia (OR 11.7, 95% CI 2.4–34.4), and hypospadias (aOR 4.8, 95% CI 2.4–9.8). We found 4 other significant associations: exposure to clonazepam and the risk of microcephaly (OR 10.2, 95% CI 2.1–30.0), exposure to phenobarbital and the risk of ventricular septal defect (OR 10.5, 95% CI 1.3–39.3), exposure to pregabalin and the risk of coarctation of aorta (OR 5.8, 95% CI 1.6–14.9), and exposure to topiramate and the risk of cleft lip with or without cleft palate (OR 6.8, 95% CI 1.4–20.0). These 4 associations were based on small numbers of cases (3, 2, 4, and 3 cases, respectively). No significant association was found for the other AEDs (table 3).

A dose-response relationship was observed for the MCMs most frequently associated with prenatal exposure to valproic acid. The highest ORs were observed in the last tertile of cumulative dose for spina bifida, atrial septal defect, cleft palate, and hypospadias. For the associations between clonazepam and microcephaly, pregabalin and coarctation of aorta, and topiramate and cleft lip with or without cleft palate, the highest ORs were also observed in the last tertile (table 4).

In the sensitivity analysis with the dispensing window reduced to the first 2 months of pregnancy, exposure to valproic acid remained associated with the same MCMs as in the main analysis, except for pulmonary valve atresia. Among the other 4 signals, exposure to clonazepam remained significantly associated with an increased risk of microcephaly. Exposure to pregabalin became associated with an increased risk of craniosynostosis, and exposure to topiramate became associated with an increased risk of hypospadias (table e-5 available from Dryad, doi.org/10.5061/dryad.qg22n65).

Discussion

This study confirmed that exposure to valproic acid during the first 2 months of pregnancy was strongly associated with a wide range of malformations among those investigated, with a dose-response relationship for half of them. This well-known teratogenicity,[7] together with the increased risk of developmental disorders for children exposed in utero,[20,21] led the European Medicines Agency to announce tighter prescription criteria for valproate-containing medicines in May 2018, including a ban during pregnancy for migraine or bipolar disorder and for epilepsy except when no other effective treatment is available,[22] whereas the US Food and Drug Administration issued a contraindication for the prevention of migraine in May 2013.[23]

The present study also found that prenatal exposure to topiramate was associated with an increased risk of cleft lip with or without cleft palate and, in the sensitivity analysis, with an increased risk of hypospadias. These results are consistent with previous findings. The first cases of oral clefts and hypospadias in infants prenatally exposed to topiramate were reported between 2006 and 2011 in studies based on small sample sizes.[24–27] Concerning hypospadias, subsequent studies based on larger sample sizes reported consistent results.[6,28,29] The association between topiramate and oral clefts was also confirmed by 1 meta-analysis[30] and other studies based on larger sample sizes comparing infants of women exposed to topiramate monotherapy to infants of women unexposed to AEDs or exposed to lamotrigine.[31–33] Compared to unexposed pregnancies, the relative risk (RR) for oral clefts associated with topiramate exposure found by Hernandez-Diaz et al.[33] was 2.69 (95% CI 1.28–5.64) and 8.30 (95% CI 2.65–26.07) when the study population was restricted to women with epilepsy and when topiramate exposure was considered with or without other anticonvulsants. The same authors reported a dose-response relationship: the median daily dose was 200 mg for women with epilepsy and 100 mg for women without epilepsy, and the RR was 1.64 (95% CI 0.53–5.07) for daily doses ≤100 mg and 5.16 (95% CI 1.94–13.73) for daily doses >100 mg. The primary RR of this study was also pooled with 6 previous studies, resulting in an RR of 5.27 (95% CI 2.88–9.65).

We observed no increased risk for any of the specific MCMs investigated in the lamotrigine- and levetiracetam-exposed groups, which is consistent with the results of other studies.[34]

Some of the other signals have already been reported. Concerning pregabalin, a first study published in 2014 did not find any

Table 2 Baseline characteristics according to AED use during the first 2 months of pregnancy

	Unexposed pregnancies, n (%)	Carbamazepine n (%)	p Value	Clonazepam n (%)	p Value	Gabapentin n (%)	p Value	Lamotrigine n (%)	p Value	Levetiracetam n (%)	p Value
Exposed pregnancies	1,875,733	512		980		365		2,997		579	
Maternal age at birth, y			< 0.0001		< 0.0001		< 0.0001		< 0.0001		NS
≤25	299,379 (16.0)	51 (10.0)		91 (9.3)		28 (7.7)		397 (13.2)		105 (18.1)	
25–30	615,395 (32.8)	121 (23.6)		239 (24.4)		89 (24.4)		953 (31.8)		191 (33.0)	
30–35	606,264 (32.3)	177 (34.6)		303 (30.9)		125 (34.2)		1,058 (35.3)		173 (29.9)	
≥35	354,695 (18.9)	163 (31.8)		347 (35.4)		123 (33.7)		589 (19.7)		110 (19.0)	
Eligibility for CMU-C	309,706 (16.5)	102 (19.9)	< 0.05	257 (26.2)	< 0.0001	81 (22.2)	< 0.05	458 (15.3)	NS	122 (21.1)	< 0.05
Year of end of pregnancy			< 0.05		< 0.0001		< 0.05		< 0.05		< 0.05
2011	299,751 (16.0)	109 (21.3)		452 (46.1)		52 (14.2)		437 (14.6)		77 (13.3)	
2012	468,491 (25.0)	123 (24.0)		406 (41.4)		78 (21.4)		706 (23.6)		120 (20.7)	
2013	487,476 (26.0)	135 (26.4)		64 (6.5)		89 (24.4)		792 (26.4)		166 (28.7)	
2014	500,961 (26.7)	114 (22.3)		48 (4.9)		113 (31.0)		865 (28.9)		172 (29.7)	
2015	119,054 (6.3)	31 (6.1)		10 (1.0)		33 (9.0)		197 (6.6)		44 (7.6)	
Folic acid supplementation	530,684 (28.3)	302 (59.0)	< 0.0001	268 (27.3)	NS	141 (38.6)	< 0.0001	2,212 (73.8)	< 0.0001	401 (69.3)	< 0.0001
Pregestational diabetes	9,333 (0.5)	6 (1.2)	< 0.05	13 (1.3)	< 0.001	15 (4.1)	< 0.0001	32 (1.1)	< 0.0001	11 (1.9)	< 0.0001
Proxy for epilepsy	2,489 (0.1)	160 (31.3)	< 0.0001	15 (1.5)	< 0.0001	19 (5.2)	< 0.0001	1,293 (43.1)	< 0.0001	308 (53.2)	< 0.0001
Hospitalization	1,884 (0.1)	96 (18.8)	< 0.0001	9 (0.9)	< 0.0001	14 (3.8)	< 0.0001	887 (29.6)	< 0.0001	210 (36.3)	< 0.0001
LTD	826 (0.0)	105 (20.5)	< 0.0001	8 (0.8)	< 0.0001	11 (3.0)	< 0.0001	680 (22.7)	< 0.0001	169 (29.2)	< 0.0001
Proxy for mood disorders	32,182 (1.7)	78 (15.2)	< 0.0001	151 (15.4)	< 0.0001	34 (9.3)	< 0.0001	294 (9.8)	< 0.0001	31 (5.4)	< 0.0001
Hospitalization	15,442 (0.8)	42 (8.2)	< 0.0001	89 (9.1)	< 0.0001	18 (4.9)	< 0.0001	186 (6.2)	< 0.0001	22 (3.8)	< 0.0001
LTD	19,211 (1.0)	57 (11.1)	< 0.0001	89 (9.1)	< 0.0001	18 (4.9)	< 0.0001	217 (7.2)	< 0.0001	12 (2.1)	< 0.05

Continued

Table 2 Baseline characteristics according to AED use during the first 2 months of pregnancy *(continued)*

	Unexposed pregnancies	Oxcarbazepine		Phenobarbital		Pregabalin		Topiramate		Valproic acid	
Exposed pregnancies	1,875,733	139		80		1,671		517		913	
Maternal age at birth (y)			< 0.05		< 0.0001		< 0.0001		< 0.05		< 0.0001
≤25	299,379 (16.0)	22 (15.8)		11 (13.8)		140 (8.4)		68 (13.2)		134 (14.7)	
25–30	615,395 (32.8)	29 (20.9)		13 (16.3)		413 (24.7)		158 (30.6)		250 (27.4)	
30–35	606,264 (32.3)	54 (38.8)		20 (25.0)		514 (30.8)		162 (31.3)		274 (30.0)	
≥35	354,695 (18.9)	34 (24.5)		36 (45.0)		604 (36.1)		129 (25.0)		255 (27.9)	
Eligibility for CMU-C	309,706 (16.5)	32 (23.0)	< 0.05	33 (41.3)	< 0.0001	425 (25.4)	< 0.0001	86 (16.6)	NS	293 (32.1)	< 0.0001
Year of end of pregnancy			< 0.05		NS		< 0.0001		< 0.05		< 0.0001
2011	299,751 (16.0)	30 (21.6)		12 (15.0)		202 (12.1)		85 (16.4)		202 (22.1)	
2012	468,491 (25.0)	46 (33.1)		25 (31.3)		358 (21.4)		116 (22.4)		283 (31.0)	
2013	487,476 (26.0)	26 (18.7)		20 (25.0)		456 (27.3)		119 (23.0)		191 (20.9)	
2014	500,961 (26.7)	27 (19.4)		18 (22.5)		510 (30.5)		147 (28.4)		199 (21.8)	
2015	119,054 (6.3)	10 (7.2)		5 (6.3)		145 (8.7)		50 (9.7)		38 (4.2)	
Folic acid supplementation	530,684 (28.3)	93 (66.9)	< 0.0001	32 (40.0)	< 0.05	458 (27.4)	NS	192 (37.1)	< 0.0001	560 (61.3)	< 0.0001
Pregestational diabetes	9,333 (0.5)	1 (0.7)	NS	2 (2.5)	< 0.05	31 (1.9)	< 0.0001	10 (1.9)	< 0.0001	7 (0.8)	NS
Proxy for epilepsy	2,489 (0.1)	56 (40.3)	< 0.0001	26 (32.5)	< 0.0001	8 (0.5)	< 0.001	64 (12.4)	< 0.0001	358 (39.2)	< 0.0001
Hospitalization	1,884 (0.1)	35 (25.2)	< 0.0001	18 (22.5)	< 0.0001	6 (0.4)	< 0.001	34 (6.6)	< 0.0001	235 (25.7)	< 0.0001
LTD	826 (0.0)	36 (25.9)	< 0.0001	12 (15.0)	< 0.0001	2 (0.1)	NS	47 (9.1)	< 0.0001	177 (19.4)	< 0.0001
Proxy for mood disorders	32,182 (1.7)	26 (18.7)	< 0.0001	11 (13.8)	< 0.0001	135 (8.1)	< 0.0001	47 (9.1)	< 0.0001	54 (5.9)	< 0.0001
Hospitalization	15,442 (0.8)	18 (12.9)	< 0.0001	5 (6.3)	< 0.0001	66 (3.9)	< 0.0001	33 (6.4)	< 0.0001	29 (3.2)	< 0.0001
LTD	19,211 (1.0)	20 (14.4)	< 0.0001	6 (7.5)	< 0.0001	91 (5.4)	< 0.0001	26 (5.0)	< 0.0001	27 (3.0)	< 0.0001

Abbreviations: AED = antiepileptic drug; CMU-C = complementary universal health insurance for low-income people; LTD = long-term disease; NS = not significant.

Table 3 Number, frequency (per 1,000 pregnancies), and ORs for the 23 selected MCMs according to the type of AEDs used during the first 2 months of pregnancy

	Unexposed pregnancies (n = 1,875,733)	Carbamazepine (n = 512)		Clonazepam (n = 980)		Gabapentin (n = 365)	
	n (‰)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Spina bifida	616 (0.33)	1 (1.95)	6.0 (0.2–33.5)	0 (0.00)	0.0 (0.0–9.3)	1 (2.74)	8.4 (0.2–47.1)
Microcephaly	438 (0.32)	1 (2.51)	7.8 (0.2–44.1)	3 (3.25)	10.2 (2.1–30.0)[a]	0 (0.00)	0.0 (0.0–39.3)
Ventricular septal defect	4643 (2.50)	0 (0.00)	0.0 (0.0–2.4)	4 (4.12)	1.7 (0.4–4.2)	1 (2.79)	1.1 (0.0–6.3)
Atrial septal defect	3268 (1.76)	0 (0.00)	0.0 (0.0–3.4)	2 (2.06)	1.2 (0.1–4.2)	0 (0.00)	0.0 (0.0–4.8)
Tetralogy of Fallot	584 (0.31)	0 (0.00)	0.0 (0.0–19.1)	1 (1.03)	3.3 (0.1–18.4)	0 (0.00)	0.0 (0.0–26.8)
Pulmonary valve atresia	152 (0.08)	0 (0.00)	0.0 (0.0–73.8)	0 (0.00)	0.0 (0.0–38.1)	0 (0.00)	0.0 (0.0–103.8)
Hypoplastic left heart syndrome	216 (0.12)	0 (0.00)	0.0 (0.0–51.8)	0 (0.00)	0.0 (0.0–26.8)	0 (0.00)	0.0 (0.0–72.8)
Hypoplastic right heart syndrome	66 (0.04)	0 (0.00)	0.0 (0.0–172.1)	0 (0.00)	0.0 (0.0–89.0)	0 (0.00)	0.0 (0.0–242.1)
Ebstein anomaly	50 (0.03)	0 (0.00)	0.0 (0.0–228.9)	0 (0.00)	0.0 (0.0–118.3)	0 (0.00)	0.0 (0.0–322.0)
Discordant ventriculoarterial connection	529 (0.28)	0 (0.00)	0.0 (0.0–21.0)	0 (0.00)	0.0 (0.0–10.9)	0 (0.00)	0.0 (0.0–29.6)
Coarctation of aorta	779 (0.42)	0 (0.00)	0.0 (0.0–14.3)	0 (0.00)	0.0 (0.0–7.4)	0 (0.00)	0.0 (0.0–20.1)
Cleft lip with or without cleft palate	1637 (0.88)	0 (0.00)	0.0 (0.0–6.8)	0 (0.00)	0.0 (0.0–3.5)	0 (0.00)	0.0 (0.0–9.5)
Cleft palate	1178 (0.63)	2 (3.98)	6.3 (0.8–22.9)	1 (1.03)	1.6 (0.0–9.1)	0 (0.00)	0.0 (0.0–13.3)
Atresia of esophagus	392 (0.21)	0 (0.00)	0.0 (0.0–28.4)	1 (1.03)	4.9 (0.1–27.4)	0 (0.00)	0.0 (0.0–40.0)
Anorectal atresia	544 (0.29)	0 (0.00)	0.0 (0.0–20.5)	0 (0.00)	0.0 (0.0–10.6)	0 (0.00)	0.0 (0.0–28.8)
Hypospadias	3371 (4.82)	2 (9.13)	1.9 (0.2–7.0)	2 (4.44)	0.9 (0.1–3.3)	1 (7.52)	1.6 (0.0–8.9)
Epispadias	82 (0.12)	0 (0.00)	0.0 (0.0–119.5)	0 (0.00)	0.0 (0.0–58.0)	0 (0.00)	0.0 (0.0–197.6)
Bilateral renal agenesis	75 (0.04)	0 (0.00)	0.0 (0.0–149.7)	0 (0.00)	0.0 (0.0–78.1)	0 (0.00)	0.0 (0.0–210.2)
Gastroschisis	243 (0.13)	0 (0.00)	0.0 (0.0–46.0)	0 (0.00)	0.0 (0.0–23.8)	0 (0.00)	0.0 (0.0–64.7)
Omphalocele	266 (0.14)	0 (0.00)	0.0 (0.0–42.0)	0 (0.00)	0.0 (0.0–21.7)	0 (0.00)	0.0 (0.0–59.1)
Diaphragmatic hernia	378 (0.20)	0 (0.00)	0.0 (0.0–29.5)	0 (0.00)	0.0 (0.0–15.2)	0 (0.00)	0.0 (0.0–41.5)
Talipes equinovarus	1677 (0.90)	0 (0.00)	0.0 (0.0–6.6)	1 (1.03)	1.1 (0.0–6.4)	0 (0.00)	0.0 (0.0–9.3)
Craniosynostosis	766 (0.41)	0 (0.00)	0.0 (0.0–14.5)	0 (0.00)	0.0 (0.0–7.5)	0 (0.00)	0.0 (0.0–20.4)

Table 3 Number, frequency (per 1,000 pregnancies), and ORs for the 23 selected MCMs according to the type of AEDs used during the first 2 months of pregnancy *(continued)*

	Lamotrigine (n = 2,997)		Levetiracetam (n = 579)		Oxcarbazepine (n = 139)		Phenobarbital (n = 80)	
	n (‰)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Spina bifida	1 (0.33)	1.0 (0.0–5.7)	0 (0.00)	0.0 (0.0–15.8)	0 (0.00)	0.0 (0.0–66.5)	0 (0.00)	0.0 (0.0–116.4)
Microcephaly	1 (0.47)	1.5 (0.0–8.2)	0 (0.00)	0.0 (0.0–23.5)	0 (0.00)	0.0 (0.0–88.0)	0 (0.00)	0.0 (0.0–163.0)
Ventricular septal defect	10 (3.37)	1.3 (0.7–2.5)	1 (1.75)	0.7 (0.0–3.9)	0 (0.00)	0.0 (0.0–8.7)	2 (25.64)	10.5 (1.3–39.3)[a]
Atrial septal defect	8 (2.70)	1.5 (0.8–3.0)	1 (1.75)	1.0 (0.0–5.6)	1 (7.19)	4.1 (0.1–23.3)	0 (0.00)	0.0 (0.0–22.2)
Tetralogy of Fallot	0 (0.00)	0.0 (0.0–3.2)	0 (0.00)	0.0 (0.0–16.8)	0 (0.00)	0.0 (0.0–69.5)	0 (0.00)	0.0 (0.0–124.9)
Pulmonary valve atresia	0 (0.00)	0.0 (0.0–12.5)	0 (0.00)	0.0 (0.0–64.9)	0 (0.00)	0.0 (0.0–269.1)	0 (0.00)	0.0 (0.0–483.5)
Hypoplastic left heart syndrome	0 (0.00)	0.0 (0.0–8.8)	1 (1.75)	15.1 (0.4–85.2)	0 (0.00)	0.0 (0.0–188.8)	0 (0.00)	0.0 (0.0–339.3)
Hypoplastic right heart syndrome	0 (0.00)	0.0 (0.0–29.1)	0 (0.00)	0.0 (0.0–151.3)	0 (0.00)	0.0 (0.0–627.6)	0 (0.00)	0.0 (0.0–1127.6)
Ebstein anomaly	0 (0.00)	0.0 (0.0–38.7)	0 (0.00)	0.0 (0.0–201.2)	0 (0.00)	0.0 (0.0–834.4)	0 (0.00)	0.0 (0.0–1499.1)
Discordant ventriculoarterial connection	0 (0.00)	0.0 (0.0–3.6)	0 (0.00)	0.0 (0.0–18.5)	0 (0.00)	0.0 (0.0–76.8)	0 (0.00)	0.0 (0.0–138.0)
Coarctation of aorta	3 (1.01)	2.4 (0.5–7.1)	1 (1.75)	4.2 (0.1–23.4)	0 (0.00)	0.0 (0.0–52.1)	0 (0.00)	0.0 (0.0–93.6)
Cleft lip with or without cleft palate	2 (0.67)	0.8 (0.1–2.8)	1 (1.75)	2.0 (0.1–11.1)	0 (0.00)	0.0 (0.0–24.7)	0 (0.00)	0.0 (0.0–44.5)
Cleft palate	2 (0.67)	1.1 (0.1–3.9)	0 (0.00)	0.0 (0.0–8.3)	0 (0.00)	0.0 (0.0–34.4)	0 (0.00)	0.0 (0.0–61.8)
Atresia of esophagus	2 (0.67)	3.2 (0.4–11.7)	0 (0.00)	0.0 (0.0–25.0)	0 (0.00)	0.0 (0.0–103.7)	0 (0.00)	0.0 (0.0–186.4)
Anorectal atresia	1 (0.34)	1.2 (0.0–6.5)	0 (0.00)	0.0 (0.0–18.0)	0 (0.00)	0.0 (0.0–74.6)	0 (0.00)	0.0 (0.0–134.1)
Hypospadias	7 (6.36)	1.2 (0.6–2.6)	0 (0.00)	0.0 (0.0–3.3)	0 (0.00)	0.0 (0.0–12.5)	0 (0.00)	0.0 (0.0–18.4)
Epispadias	1 (0.91)	7.7 (0.2–44.5)	0 (0.00)	0.0 (0.0–139.4)	0 (0.00)	0.0 (0.0–524.6)	0 (0.00)	0.0 (0.0–774.5)
Bilateral renal agenesis	0 (0.00)	0.0 (0.0–25.5)	0 (0.00)	0.0 (0.0–132.3)	0 (0.00)	0.0 (0.0–555.7)	0 (0.00)	0.0 (0.0–973.0)
Gastroschisis	2 (0.67)	5.2 (0.6–18.9)	0 (0.00)	0.0 (0.0–40.4)	0 (0.00)	0.0 (0.0–167.7)	0 (0.00)	0.0 (0.0–301.3)
Omphalocele	1 (0.34)	2.4 (0.1–13.3)	0 (0.00)	0.0 (0.0–36.9)	0 (0.00)	0.0 (0.0–153.1)	0 (0.00)	0.0 (0.0–275.1)
Diaphragmatic hernia	1 (0.34)	1.7 (0.0–9.3)	0 (0.00)	0.0 (0.0–25.9)	0 (0.00)	0.0 (0.0–107.6)	0 (0.00)	0.0 (0.0–193.3)
Talipes equinovarus	2 (0.67)	0.7 (0.1–2.7)	1 (1.75)	1.9 (0.0–10.9)	0 (0.00)	0.0 (0.0–24.2)	0 (0.00)	0.0 (0.0–43.4)
Craniosynostosis	0 (0.00)	0.0 (0.0–2.5)	1 (1.75)	4.2 (0.1–23.8)	0 (0.00)	0.0 (0.0–53.0)	0 (0.00)	0.0 (0.0–95.2)

Continued

Table 3 Number, frequency (per 1,000 pregnancies), and ORs for the 23 selected MCMs according to the type of AEDs used during the first 2 months of pregnancy (continued)

	Pregabalin (n = 1,671)		Topiramate (n = 517)		Valproic acid (n = 913)	
	n (‰)	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Spina bifida	1 (0.60)	1.8 (0.0–10.2)	0 (0.00)	0.0 (0.0–17.7)	6 (6.57)	19.4 (8.6–43.5)[a]
Microcephaly	0 (0.00)	0.0 (0.0–8.3)	1 (2.88)	9.0 (0.2–50.8)	0 (0.00)	0.0 (0.0–13.1)
Ventricular septal defect	5 (3.02)	1.1 (0.5–2.8)	2 (3.98)	1.6 (0.2–5.8)	9 (10.20)	4.0 (2.1–7.8)[a]
Atrial septal defect	6 (3.63)	1.9 (0.8–4.1)	2 (3.98)	2.3 (0.3–8.2)	15 (17.01)	9.0 (5.4–15.0)[a]
Tetralogy of Fallot	0 (0.00)	0.0 (0.0–5.8)	0 (0.00)	0.0 (0.0–19.1)	2 (2.27)	7.2 (0.9–26.3)
Pulmonary valve atresia	0 (0.00)	0.0 (0.0–22.4)	0 (0.00)	0.0 (0.0–73.8)	2 (2.27)	27.8 (3.3–102.5)[a]
Hypoplastic left heart syndrome	1 (0.60)	5.2 (0.1–29.4)	0 (0.00)	0.0 (0.0–51.8)	2 (2.27)	19.6 (2.4–71.7)[a]
Hypoplastic right heart syndrome	0 (0.00)	0.0 (0.0–52.3)	0 (0.00)	0.0 (0.0–172.1)	0 (0.00)	0.0 (0.0–98.0)
Ebstein anomaly	0 (0.00)	0.0 (0.0–69.5)	0 (0.00)	0.0 (0.0–228.9)	0 (0.00)	0.0 (0.0–130.4)
Discordant ventriculoarterial connection	0 (0.00)	0.0 (0.0–6.4)	0 (0.00)	0.0 (0.0–21.0)	0 (0.00)	0.0 (0.0–12.0)
Coarctation of aorta	4 (2.42)	5.8 (1.6–14.9)[a]	0 (0.00)	0.0 (0.0–14.3)	0 (0.00)	0.0 (0.0–8.1)
Cleft lip with or without cleft palate	1 (0.60)	0.7 (0.0–3.8)	3 (5.96)	6.8 (1.4–20.0)[a]	3 (3.40)	3.9 (0.8–11.4)
Cleft palate	2 (1.21)	1.9 (0.2–6.9)	0 (0.00)	0.0 (0.0–9.4)	3 (3.40)	5.4 (1.1–15.8)[a]
Atresia of esophagus	0 (0.00)	0.0 (0.0–8.6)	1 (1.99)	9.4 (0.2–53.2)	0 (0.00)	0.0 (0.0–16.2)
Anorectal atresia	1 (0.60)	2.1 (0.1–11.6)	0 (0.00)	0.0 (0.0–20.5)	3 (3.40)	11.7 (2.4–34.4)[a]
Hypospadias	2 (3.40)	0.7 (0.1–2.6)	3 (16.39)	3.4 (0.7–10.2)	8 (22.92)	4.8 (2.4–9.8)[a]
Epispadias	0 (0.00)	0.0 (0.0–44.2)	0 (0.00)	0.0 (0.0–143.2)	0 (0.00)	0.0 (0.0–74.8)
Bilateral renal agenesis	0 (0.00)	0.0 (0.0–45.8)	0 (0.00)	0.0 (0.0–148.3)	0 (0.00)	0.0 (0.0–83.9)
Gastroschisis	0 (0.00)	0.0 (0.0–14.0)	0 (0.00)	0.0 (0.0–46.0)	0 (0.00)	0.0 (0.0–26.2)
Omphalocele	0 (0.00)	0.0 (0.0–12.7)	0 (0.00)	0.0 (0.0–42.0)	0 (0.00)	0.0 (0.0–23.9)
Diaphragmatic hernia	0 (0.00)	0.0 (0.0–9.0)	1 (1.99)	9.8 (0.2–55.2)	0 (0.00)	0.0 (0.0–16.8)
Talipes equinovarus	0 (0.00)	0.0 (0.0–2.0)	1 (1.99)	2.2 (0.1–12.4)	0 (0.00)	0.0 (0.0–3.8)
Craniosynostosis	3 (1.81)	4.4 (0.9–13.0)	0 (0.00)	0.0 (0.0–14.5)	2 (2.27)	5.5 (0.7–20.0)

Abbreviation: AED = antiepileptic drug; CI = confidence interval; MCM = major congenital malformation; OR = odds ratio.
For MCMs with <5 cases per treatment group, crude ORs with exact CIs are reported. For MCMs with >5 cases per treatment group, adjusted ORs are reported.
[a] ORs for which the 95% CI does not include 1.

Table 4 Number, frequency (per 1,000 pregnancies), and crude ORs according to tertiles of cumulative dose

	Tertile 1[a]		Tertile 2[b]		Tertile 3[c]	
	n (‰)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Valproic acid						
Spina bifida	0 (0)	0.0 (0.0–30.4)	1 (3.26)	9.9 (0.3–56.0)	5 (16.45)	50.9 (16.4–120.8)
Ventricular septal defect	2 (6.85)	2.8 (0.3–10.0)	4 (13.33)	5.4 (1.5–14.0)	3 (10.34)	4.2 (0.9–12.3)
Atrial septal defect	2 (6.85)	3.9 (0.5–14.3)	5 (16.67)	9.6 (3.1–22.7)	8 (27.59)	16.1 (6.9–32.2)
Pulmonary valve atresia	1 (3.42)	42.0 (1.1–239.6)	0 (0.00)	0.0 (0.0–124.0)	1 (3.45)	42.3 (1.1–241.2)
Hypoplastic left heart syndrome	0 (0.00)	0.0 (0.0–89.4)	2 (6.67)	57.8 (6.9–213.0)	0 (0.00)	0.0 (0.0–90.0)
Cleft palate	0 (0.00)	0.0 (0.0–16.3)	1 (3.33)	5.3 (0.1–29.7)	2 (6.90)	11.0 (1.3–40.0)
Anorectal atresia	1 (3.42)	11.7 (0.3–66.2)	1 (3.33)	11.4 (0.3–64.4)	1 (3.45)	11.8 (0.3–66.7)
Hypospadias	1 (7.81)	1.6 (0.0–9.2)	0 (0.00)	0.0 (0.0–5.6)	7 (64.22)	14.2 (5.5–30.3)
Clonazepam						
Microcephaly	1 (3.14)	9.8 (0.2–55.5)	0 (0.00)	0.0 (0.0–31.7)	2 (6.47)	20.3 (2.4–74.5)
Phenobarbital						
Ventricular septal defect	1 (37.04)	15.4 (0.4–93.6)	1 (40.00)	16.6 (0.4–102.1)	0 (0.00)	0.0 (0.0–48.8)
Pregabalin						
Coarctation of aorta	1 (1.83)	4.4 (0.1–24.6)	1 (1.83)	4.4 (0.1–24.5)	2 (3.57)	8.5 (1.0–31.1)
Topiramate						
Cleft lip with or without cleft palate	1 (6.00)	6.8 (0.2–38.7)	0 (0.00)	0.0 (0.0–20.9)	2 (11.63)	13.4 (1.6–49.0)

Abbreviations: CI = confidence interval; OR = odds ratio
[a] Tertile 1: valproic acid ≤26,667 mg, clonazepam ≤40 mg, phenobarbital ≤3,000 mg (50 mg/d), pregabalin ≤1,820 mg, and topiramate ≤1,447 mg.
[b] Tertile 2: valproic acid 26,667 to 48,000 mg, clonazepam 40 to 50 mg, phenobarbital 3,000 to 5,100 mg, pregabalin 1,820 to 4,387 mg, and topiramate 1,447 to 3,400 mg.
[c] Tertile 3: valproic acid >48,000 mg, clonazepam >50 mg, phenobarbital >5,100 mg, pregabalin >4,387 mg, and topiramate >3,400 mg.

increased risk of MCMs among 30 prenatally exposed children,[1] and a more recent study found 1 case of ventricular septal defect among 14 exposed children.[35] Larger studies have also been conducted. In 1 study, the results of which may be prone to confounding, exposure to pregabalin was associated with an increased risk of birth defects, including cardiac malformations,[36] but this association was not confirmed by a larger, better-designed study.[37] Exposure to phenobarbital has also been shown to be associated with an increased risk of birth defects, with a higher frequency of cardiac malformations compared to other malformations.[38] However, the associations between clonazepam and microcephaly and between valproic acid and both pulmonary valve and anorectal atresia have never been previously reported.

This first nationwide cohort study based on the French health care databases designed to assess drug safety during pregnancy has a number of strengths. Accurate identification of pregnancy periods should have limited misclassification of medication exposure during pregnancy.[4] The increased risks of malformations observed in this study cannot be attributed to other known teratogenic medications or infections because only AED monotherapy was considered and women with concomitant teratogenic medications or infections were excluded. Almost 1.9 million pregnancies were included in the cohort, allowing a wide range of specific MCMs and AED classes to be studied. A large number of these associations have not been previously studied.[34] This study therefore contributes to a better knowledge of AED use during pregnancy, which should guide prescribing decisions by allowing prescribers to compare the teratogenicity of an individual woman's treatment with alternative treatments.

However, this study has several limitations. First, exposure assessment was based on pharmacy claims, which do not indicate how the patient actually takes the medication. Although the time period during which a woman is pregnant was accurately identified, we cannot rule out exposure misclassification, especially for AED classes that are often discontinued before conception,[39] which could explain why certain associations were no longer significant in the sensitivity analysis in which the dispensing window was reduced to the first 2 months of pregnancy. In particular, pregabalin was often discontinued before conception; the number of women exposed decreased from 1,671 (table 2) to 918 (table e-5 available from Dryad, doi. org/10.5061/dryad.qg22n65) when the dispensing window was reduced to the first 2 months of pregnancy.

Second, despite the use of a large cohort of almost 1.9 million pregnancies, only a small number of women were exposed to certain AEDs such as gabapentin or oxcarbazepine, and no clear safety conclusions can be drawn on the basis of the absence of signal from these exposure classes. Moreover, most of the signals identified were based on a small number of cases and should therefore be interpreted with appropriate caution.[18] False-positive signals due to multiple testing also cannot be ruled out.

Third, even for MCMs with at least 5 cases per treatment group, residual confounding cannot be excluded, although the role of confounding in the assessment of AED teratogenicity has been reported to be limited.[6] Over-the-counter folic acid supplements were not captured in the databases. However, given the high frequencies of folic acid supplementation observed in the cohort, particularly among women exposed to lamotrigine, levetiracetam, or oxcarbazepine, over-the-counter folic acid supplements should represent a small proportion of all folic acid dispensed. In addition, we could not adjust ORs for parental history of MCMs because this information is not available in the French health care databases. Although alcohol intake is also not available, we developed a modified version of an algorithm from a previously published study[40]: we constructed a proxy for alcohol intake in the year before pregnancy or during pregnancy on the basis of drug dispensing, hospital discharge diagnoses, LTD diagnoses, and the child's hospital discharge diagnoses at birth (table e-4 available from Dryad, doi.org/10.5061/dryad.qg22n65). This algorithm identified only 0.3% of women with alcohol-related diagnoses or drug reimbursements in the study cohort. In addition, because alcohol-related diagnoses are often coded at the same time as malformations, differential misclassification of alcohol intake cannot be ruled out, which is why, in this context, we did not use this proxy to adjust ORs for alcohol intake. However, we calculated e-values to assess the robustness of our results to potential unmeasured or uncontrolled confounding.[41] Given the strength of the associations between the risk of MCMs and parental history of MCMs[6] and alcohol intake[42,43] found in the literature, it is unlikely that these factors could individually fully explain most of the observed ORs according to the e-values (table e-6 available from Dryad, doi.org/10.5061/dryad.qg22n65).

In addition, some AEDs are indicated for the treatment of not only epilepsy but also psychiatric disorders, pain, migraine, etc. In particular, the results of this study suggest that pregabalin, clonazepam, and gabapentin were marginally prescribed for the treatment of epilepsy. However, the French health care databases do not contain medical indications other than LTD and hospital discharge diagnosis ICD-10 codes, and these indications cannot be exhaustively assessed, which is why we did not limit the study population to women with epilepsy. However, it is now widely accepted that malformations are associated with the use of AEDs during pregnancy rather than with the underlying maternal illness being treated.[44]

Fourth, because the study outcomes were limited to a list of 23 MCMs, no conclusion can be drawn concerning all of the other MCMs. We also cannot rule out outcome misclassification because diagnoses and medical procedure codes used to identify the 23 selected MCMs in the PMSI database have not been externally validated. However, the PMSI database is used for planning and funding purposes and is subject to coding quality control. We also carefully identified the 23 selected MCMs in collaboration with an expert working group and, when necessary, required diagnoses to be followed by a medical procedure. The fact that MCMs known to be associated with valproic acid were also found to be associated with valproic acid in this study should increase confidence in the definition of these outcomes.

Differences between exposure groups, in terms of pregnancy management and especially in terms of screening, could also constitute another limitation regarding outcomes. More frequent screening for malformations among exposed mothers and babies could have resulted in overestimation of the association between AED exposure and the risk of malformations. However, when screening is performed before birth and results in therapeutic abortion, these associations would be biased in the opposite direction because data on malformations are not available for therapeutic abortions <22 weeks after the last menstrual period and are incomplete for therapeutic abortions ≥22 weeks after the last menstrual period[18]. If prenatal screening were performed more frequently among women exposed to AEDs during pregnancy, it would have resulted in underestimation of the association between AED exposure and the risk of severe malformations with a high propensity for termination of pregnancy.

Despite the limitations inherent to health care claims databases, this study highlights the importance of these data in assessing drug safety during pregnancy. It confirms the teratogenicity of valproic acid and the probable association between prenatal exposure to topiramate and the risk of cleft lip with or without cleft palate and hypospadias. These results also suggest that prenatal exposures to clonazepam, phenobarbital, and pregabalin were associated with an increased risk of 1 specific MCM, but as a result of possible exposure misclassification or confounding and small numbers of cases, these associations need to be interpreted with caution and confirmed by in-depth studies with a sample size allowing more definitive conclusions.

Disclosure

Acknowledgment

Appendix Authors

Name	Location	Role	Contribution
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Alain Weill, MD	French National Health Insurance (CNAM), Paris, France	Author	Study conception and design, interpretation of data, critical revision of the manuscript for intellectual content
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Appendix (continued)

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