Antiepileptic drugs and intrauterine death

A prospective observational study from EURAP

Torbjörn Tomson, MD*
Dina Battino, MD*
Erminio Bonizzoni, PhD
John J. Craig, MD
Dick Lindhout, MD
Emilio Perucca, MD
Anne Sabers, MD
Sanjeev V. Thomas, MD
Frank Vajda, MD
For the EURAP Study Group

Correspondence to Dr. Tomson: torbjorn.tomson@karolinska.se

ABSTRACT

Objective: To compare the risk of spontaneous abortions and stillbirth associated with maternal use of different antiepileptic drugs (AEDs).

Methods: The EURAP registry is an observational international cohort study primarily designed to determine the risk of major congenital malformations (MCMs) after prenatal AED exposure. Using EURAP data, we prospectively monitored pregnancies exposed to the 6 most common AED monotherapies and to polytherapy. Intrauterine death (spontaneous abortion and stillbirth combined) was the primary endpoint.

Results: Of 7,055 pregnancies exposed to monotherapy with lamotrigine (n = 1,910), carbamazepine (n = 1,713), valproic acid (n = 1,171), levetiracetam (n = 324), oxcarbazepine (n = 262), or phenobarbital (n = 260), and to polytherapy (n = 1,415), 632 ended in intrauterine deaths (592 spontaneous abortions and 40 stillbirths). Rates of intrauterine death were similar across the different monotherapies (8.2%; 95% confidence interval [CI] 7.5%–8.9%), higher with polytherapy (12.1%; 95% CI 10.5%–13.9%), but showed no relationship with AED dose in monotherapy at conception. Multivariable analysis including 11 covariates in addition to the different AED exposures showed that the risk was greater with polytherapy vs monotherapy (risk ratio [RR] 1.38; 95% CI 1.14–1.66), parental history of MCMs (RR 1.92; 1.20–3.07), maternal age (RR 1.06; 1.04–1.07), and number of previous intrauterine deaths (RR 1.09; 1.00–1.19). The risk was greater with early enrollment and decreased with later gestational week at enrollment (RR 0.84; 0.82–0.86).

Conclusions: The most important risk factors for intrauterine death in pregnancies of women with epilepsy include maternal exposure to AED polytherapy and the presence of MCMs in at least one of the parents. ***Neurology*® 2015;85:580–588**

GLOSSARY

AED = antiepileptic drug; **CBZ** = carbamazepine; **CI** = confidence interval; **EURAP** = International Registry of Antiepileptic Drugs and Pregnancy; **LTG** = lamotrigine; **MCM** = major congenital malformation; **RR** = risk ratio; **VPA** = valproic acid.

Ever since the first report of major congenital malformations (MCMs) in the offspring of women taking antiepileptic drugs (AEDs) in pregnancy,[1] research has been dedicated to the assessment of teratogenic risks associated with AEDs. Concerns focused primarily on the risk of MCMs[2,3] and, more recently, on impaired cognitive and behavioral development after prenatal AED exposure.[4,5] Registries set up in the late 1990s have enrolled thousands of pregnancies and enabled comparisons of MCM rates between different AEDs at different dose levels.[6–9] Other observational studies have revealed differences in postnatal cognitive development.[5] For both

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*These authors contributed equally to this work.

From the Department of Clinical Neuroscience (T.T.), Karolinska Institutet, Stockholm, Sweden; Epilepsy Center (D.B.), Department of Neurophysiology and Experimental Epileptology, IRCCS Neurological Institute Carlo Besta Foundation, Milan; Department of Clinical Science and Community (E.B.), Section of Medical Statistics and Biometry G.A. Maccacaro, Faculty of Medicine and Surgery, University of Milan, Italy; Belfast Health and Social Care Trust (J.J.C.), Belfast, Ireland; Department of Medical Genetics (D.L.), University Medical Center Utrecht; SEIN–Epilepsy Institute in the Netherlands Foundation (D.L.), Hoofddorp, the Netherlands; Department of Internal Medicine and Therapeutics (E.P.), University of Pavia, and Clinical Trial Center, C. Mondino National Neurological Institute, Pavia, Italy; The Epilepsy Clinic (A.S.), Department of Neurology, Rigshospitalet University State Hospital, Copenhagen, Denmark; Department of Neurology (S.V.T.), Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala, India; and Departments of Medicine and Neurology (F.V.), University of Melbourne, Royal Melbourne Hospital, Australia.

EURAP Study Group coinvestigators and contributors are listed on the *Neurology*® Web site at Neurology.org.

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types of outcomes, valproic acid (VPA) has been shown to be associated with greater risks than other AEDs, such as carbamazepine (CBZ) and lamotrigine (LTG), and additional AEDs in a dose-related manner.[7–9]

Less focus has been given to the role of AEDs regarding other adverse pregnancy outcomes, in particular spontaneous abortions and stillbirths. A recent Danish study based on data from national health registries found no association between AED use during pregnancy and spontaneous abortions in women with epilepsy (n = 2,615) but found a significantly increased risk with AED use in women without epilepsy,[10] leading to the question of a potential impact of unmeasured confounding.

We have used data from EURAP, an international AEDs and pregnancy registry, to assess the relationship between different AED treatments and the risk of spontaneous abortions and stillbirths in a cohort of more than 7,000 prospectively followed pregnancies of women with epilepsy on AED treatment, for whom more details on other risk factors and potential confounders were available compared with the Danish study.

METHODS

The EURAP methodology, which has previously been described in detail,[7] is summarized below.

Eligibility criteria and study procedures. The principal aim of EURAP is to compare the risk of MCMs in pregnancies exposed to AEDs.[7] The present study evaluates the comparative risk of intrauterine death (spontaneous abortions and stillbirths) in women enrolled in the EURAP study and who were exposed to the 6 most frequently used monotherapies (CBZ, LTG, VPA, phenobarbital, levetiracetam, and oxcarbazepine) and AED polytherapy.

Cases, defined as prospective and suitable for inclusion in the EURAP study, are pregnancies exposed to AEDs, taken at the time of conception, and identified before the outcome of the pregnancy is known and no later than the end of the 16th week of gestation. Data on maternal demographics, epilepsy and seizure types, including frequency of seizures, presence of comorbidities, and family history of MCMs, prior pregnancies resulting in intrauterine death, other drug exposures, to include folate and exposure to other teratogens in pregnancy such as smoking, alcohol, and other potential risk factors are collected at registration and throughout pregnancy. Data on seizure control and changes in treatment are recorded at the end of each trimester with pregnancy outcome collected at birth and 1 year postdelivery. At all stages, information is collected by the reporting physician, before being forwarded to a national coordinator who then sends it to the central database in Milan, Italy.

The EURAP registry was founded in 1999. It presently receives cases from more than 900 collaborators from 42 countries. For the present analysis, a cutoff date of May 24, 2013, was arbitrarily established, at which point 18,353 pregnancies had been registered.

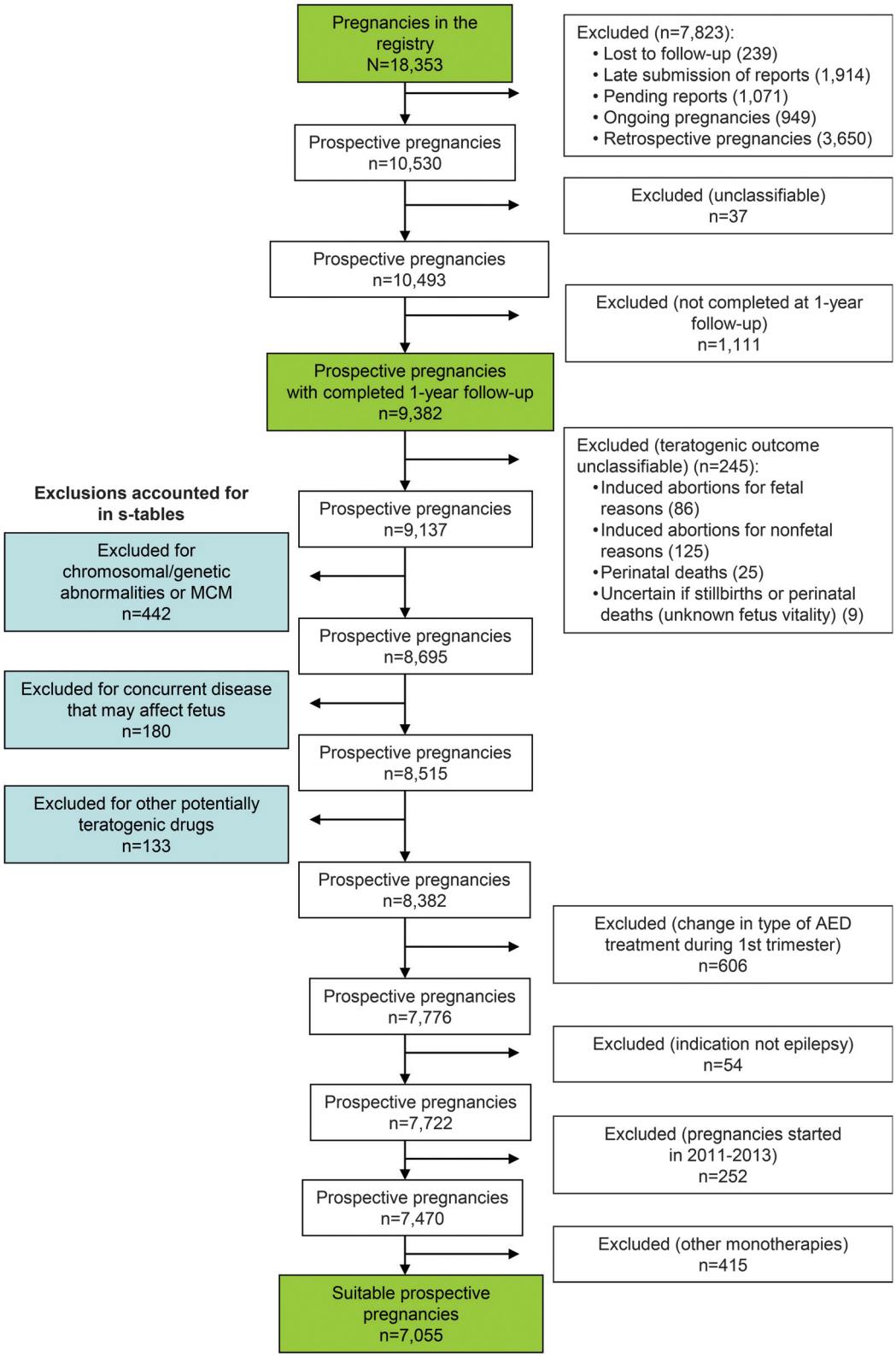
Exclusions. Pregnancies that were identified retrospectively or occurred in women without epilepsy, that were lost to follow-up, or for which data were not submitted within preset deadlines, because of a concern that these cases night not be considered truly prospective, and for which follow-up had not been completed, were excluded. Pregnancies were also excluded if AEDs were changed or withdrawn during the first trimester, if pregnancies were exposed to other potentially teratogenic drugs, and when they occurred with comorbidities that could increase the risk of MCMs or miscarriage (e.g., diabetes, toxoplasmosis, and HIV infection). Pregnancies resulting in live offspring with MCMs, chromosomal or genetic abnormalities, perinatal deaths (here defined as a death within 7 days after birth in a live born baby after week 24 gestation), and induced abortions were also excluded. Finally, because of the small numbers involved, we excluded pregnancies exposed to all other AEDs taken in monotherapy. The exclusion process is illustrated in the figure.

Definition of drug exposure and covariates. Pregnancies were defined by type and dose of AED at the time of conception. We used a conservative approach that mimics the intention-to-treat principle of controlled clinical trials. As such, for pregnancies in which AED dose was altered in pregnancy, analysis was based on the dose at the time of conception and did not take account of any subsequent changes in dose. Seizures were classified as generalized tonic-clonic ("convulsive seizures") or other types with the type of epilepsy being classified according to International League Against Epilepsy criteria from 1989 (Commission 1989)[11] as localization-related epilepsy, which is equivalent to focal epilepsy and as idiopathic generalized epilepsy, which is equivalent to genetic generalized epilepsy in the latest proposed terminology.[12] Parental history of MCMs excluded those with cerebral malformations as the cause of the maternal epilepsy. Folate intake was defined as being appropriate, irrespective of dose, if it had been started at least 3 months before conception and had been continued through the first trimester. Parental educational levels were recorded as low (illiterate or primary school only) or medium/high (secondary or tertiary school).

Outcome. For the purposes of this study, spontaneous abortions were defined as intrauterine deaths occurring after enrollment in the registry and before the 24th gestational week. Those occurring later in pregnancy were designated stillbirths following the recommendations of the Perinatal Institute UK (http://www.perinatal.nhs.uk/definitions). We are aware that suggested cutoffs between spontaneous abortion and stillbirth vary considerably and have also changed over time. For our primary analysis, these 2 outcomes were combined into one, which we categorized as intrauterine death. Perinatal mortality was defined as neonatal deaths during the first week after delivery from gestational week 24. These were not included in our analyses but are reported descriptively.

Statistical analysis. To achieve a >90% power (2-sided 0.05 significance level) of detecting a risk ratio (RR) ≥1.5, a total sample of 7,000 observations is required. This is calculated on a log-binomial regression of a binary response variable on a binary covariate with a prevalence ranging from 10% to 90% and an 8% rate of abortion events in the reference group. We used the EURAP dose-categorization algorithm[7] to split each AED

Figure Flowchart for selection process



Flowchart describing the selection process for the present analysis of intrauterine deaths. AED = antiepileptic drug; MCM = major congenital malformation.

treatment into dose categories. The Cochran-Armitage test was used to investigate for the presence of a dose response across the identified categories. To calculate intrauterine death rates, the sum of all pregnancies with confirmed intrauterine death was the numerator and the sum of all eligible exposed cases was the denominator. A random effect log-binomial model[13] was used to compare treatments (the 6 monotherapies and polytherapy) after adjusting for potential confounders or prognostic factors

(maternal age, educational level of mother and father, family history of epilepsy, parental history of MCMs, parity, number of previous intrauterine deaths, type of epilepsy, gestational age at inclusion in the registry, major convulsive seizures during first trimester, folic acid use) and to assess the effect of these factors on prognosis. Log-binomial regression was performed by fitting data through a generalized mixed linear model with log-link function, binomial distribution, and indicator of mother as random effect in order to adjust estimates for the presence of clustered data (women with more than one birth).

The expected-maximization algorithm[14] was used to replace missing values for covariates. Results are reported as RRs with associated 2-tailed 95% confidence intervals (CIs) and p values. All statistical calculations were performed with SAS version 9.2 (SAS Institute, Cary, NC).

Standard protocol approvals, registrations, and patient consents. The EURAP protocol was approved by the ethics committees of all participating centers. Informed consent was obtained from all women, either in writing or orally depending on local requirements.

RESULTS A total of 7,055 pregnancies met the criteria for analysis. Demographic and clinical data for this cohort are presented in table 1. Within the cohort, 6,146 women contributed to these pregnancies with 720 women contributing with 2 pregnancies (77 of which were twin pregnancies), 81 with 3 (14 twins and 2 triplets), and 9 with 4 pregnancies. The median time of enrollment in the registry was the eighth gestational week. These pregnancies resulted in 592 spontaneous abortions (8.4% of all pregnancies) and 40 stillbirths (0.6% of the pregnancies). Their distribution according to AED treatment is summarized in table 2. Intrauterine death rates were very similar across the included monotherapies, ranging from 7.9% (95% CI 6.7%–9.2%) with LTG to 8.6% (5.8%–12.3%) for levetiracetam (table 3). There was no significant association between dose level at time of conception and risk of intrauterine death for any of the 3 AEDs (LTG, CBZ, VPA) for which sample size was sufficient to test relationship with dose. The rate of intrauterine death associated with polytherapy was higher, at 12.1% (10.4%–13.9%).

Table 4 shows a comparison of the 7 treatment categories (6 monotherapies and polytherapy) after adjustment for potential confounders or prognostic factors using the random-effects log-binomial model. There was no difference in risk of intrauterine death between the 6 monotherapies, while polytherapy was associated with a significantly increased risk compared with all monotherapies combined, with an RR of 1.4 (1.1–1.7). Other parameters associated with increased risk were type of epilepsy (undetermined/unclassifiable vs idiopathic generalized), gestational week at enrollment in EURAP (the earlier the enrollment the greater the risk), maternal age (the older the woman the greater the risk), number of previous pregnancies with intrauterine deaths (increasing risk with increasing numbers), and a parental history of MCMs. The latter was the strongest risk factor, with an RR of 1.92 (1.20–3.07). There were 15 of 632 (2.4%) pregnancies ending in intrauterine death in which at least one of the parents had a known MCM compared with 72 of 6,423 (1.1%) pregnancies ending with delivery. One woman contributed 3 such pregnancies and another woman 2 pregnancies with intrauterine death. The specific MCMs are listed in table e-1 on the *Neurology*® Web site at Neurology.org, with 5 involving malformations of the uterus and 14 of 15 pregnancies associated with maternal MCM. There were 32 cases with convulsive status epilepticus and 16 with nonconvulsive status during pregnancy. One of the pregnancies with convulsive status ended in a stillbirth, but otherwise there were no intrauterine deaths.

As discussed in the methods section, pregnancies with live births in which the offspring died within the first 7 days (perinatal deaths) were not included in the analysis. There were 15 such perinatal deaths out of 7,070 (7,055 + 15) prospective pregnancies that met eligibility criteria for the present study. Further information on the clinical characteristics of pregnancies associated with perinatal deaths is summarized in table e-2.

DISCUSSION Spontaneous abortions and stillbirth are not only important adverse outcomes per se, but also potential expression of teratogenic effects. Therefore, any effect of AED exposure on the risk of intrauterine death could affect the frequency of MCMs detected after birth. Given this background, it is surprising that only one study to date (the Danish register study) has evaluated the comparative risks of intrauterine death associated with different AED treatments.[10] Our findings in a considerably larger cohort of prospectively followed pregnancies in women with epilepsy demonstrate that frequencies of intrauterine death are similar across pregnancies exposed to the 6 most frequently used AED monotherapies, in keeping with the results of the Danish study.[10] We found no relationship between occurrence of intrauterine death and AED dose, at least for LTG, CBZ, or VPA, whereas an increased occurrence was identified in women exposed to polytherapy. The observation that AED monotherapy, which is the predominant treatment regimen in pregnant women with epilepsy,[7–9] had no apparent impact on the rate of spontaneous abortions or stillbirths is also consistent with a previous report from Rochester based on 788 pregnancies in 256 women with epilepsy.[15] That study found no difference in rates of spontaneous abortions between pregnancies of women with epilepsy on (14.6%) or off (13.6%) AED medication or between pregnancies of women

Table 1 Demographics and clinical data of pregnancies included (n = 7,055)

Maternal age at time of enrollment, y	29.9 (14.1–46.6)
Duration of pregnancy at time of enrollment, wk	8 (1–16)
Parent history of major congenital malformations	
Negative	6,936 (98.3)
Positive	87 (1.2)
Information missing	32 (0.5)
Geographical region	
Americas	80 (1.1)
Europe	6,075 (86.1)
Southeast Asia	235 (3.3)
Western Pacific	665 (9.4)
Parity	
0	4,228 (59.9)
1	2,247 (31.8)
2	450 (6.4)
≥3	125 (1.8)
Information missing	5 (0.1)
Type of epilepsy	
Idiopathic generalized epilepsy[a]	2,543 (36.1)
Localization-related epilepsy[a]	3,677 (52.1)
Undetermined/unclassifiable	835 (11.8)
Convulsive seizures during the first trimester	
No	6,367 (90.3)
Yes	664 (9.4)
Information missing	24 (0.3)
Educational level of the father[b]	
Low	1,101 (15.6)
Medium or high	5,304 (75.2)
Information missing	650 (9.2)
Educational level of the mother[b]	
Low	1,027 (14.6)
Medium or high	5,534 (78.4)
Information missing	494 (7.0)
Folic acid use[c]	
Appropriate	2,567 (36.4)
Inappropriate	4,450 (63.1)
Information missing	38 (0.5)
Previous spontaneous abortions/ stillbirths	
0	5,635 (79.9)
1	1,025 (14.5)
2	279 (4.0)
≥3	115 (1.6)
Information missing	1 (0.01)
Pregnancies	
Singleton	6,867 (97.3)
Twins	182 (2.6)
Triplets	6 (0.1)

Data are median (range) or n (%).
[a] Localization-related is equivalent to focal, and idiopathic generalized is in most cases equivalent to genetic generalized epilepsy in the new terminology.[12]
[b] Educational level is low for an illiteracy or primary level and medium or high for secondary or tertiary level.
[c] Folic acid is appropriate if taken continuously at least 3 months before conception up to 3 months after conception; otherwise, it is inappropriate.

with epilepsy and pregnancies of spouses of men with epilepsy. In the general population in the Danish register study, the rate of spontaneous abortions is 11% and of stillbirths is 0.3%.[10] However, the rates of spontaneous abortions identified in our analysis cannot be compared with those of the Rochester study or the Danish register study because, in addition to using slightly different diagnostic criteria, our prospective study did not allow detection of early abortions occurring before enrollment (median gestational week 8), while the Rochester medical record linkage system and the Danish Health Care register enabled identification of abortions occurring throughout the entire duration of pregnancy. The Rochester study also found that in women with epilepsy, as in the general population, the highest rates of spontaneous abortion occur in early pregnancy,[15] which is in line with our own findings showing decreasing risk of intrauterine death with increasing gestational week (table 4). Gestational age at enrollment in EURAP was included in the multivariable analysis because it could potentially be a confounder if there were systematic differences between treatments in time of enrollment. The observation that the risk of intrauterine death in our cohort increased with maternal age is also in agreement with earlier findings in women with epilepsy[15] and in the general population.[16] Finally, our observation that major convulsive seizures had no identifiable influence on abortions and stillbirths is consistent with earlier data suggesting that the rate of spontaneous abortions is not increased among women with epilepsy.[15]

The recent Danish register–based study has some advantages.[10] Because it is population-based, its results are representative of and the methodology allows a comparison with the general population. It is therefore reassuring that the absence of differences in miscarriage rates among different AEDs in our more selected population is consistent with the Danish findings. The strength of our study, in addition to

Table 2 Number of spontaneous abortions and stillbirths by antiepileptic treatment

Antiepileptic drug	Total	Delivered	Spontaneous abortions	Stillbirths	Spontaneous abortions and stillbirths
Lamotrigine	1,910	1,760 (92.1)	144 (7.5)	6 (0.3)	150 (7.8)
Carbamazepine	1,713	1,569 (91.6)	130 (7.6)	14 (0.8)	144 (8.4)
Valproic acid	1,171	1,076 (91.9)	90 (7.7)	5 (0.4)	95 (8.1)
Levetiracetam	324	296 (91.4)	27 (8.3)	1 (0.3)	28 (8.6)
Oxcarbazepine	262	240 (91.6)	20 (7.6)	2 (0.8)	22 (8.4)
Phenobarbital	260	238 (91.5)	20 (7.7)	2 (0.8)	22 (8.5)
Polytherapy[a]	1,415	1,244 (87.9)	161 (11.4)	10 (0.7)	171 (12.1)

Data are n (%).
[a] There were 208 different combinations. The most common polytherapies were lamotrigine and valproic acid (n = 153), lamotrigine and levetiracetam (n = 105), lamotrigine and carbamazepine (n = 84), carbamazepine and levetiracetam (n = 77), and carbamazepine and phenobarbital (n = 54).

its unparalleled size, is that it includes more detailed information on other potential risk factors that could confound the results, e.g., family history of epilepsy and MCMs, previous pregnancy losses, types of epilepsy, seizures during pregnancy, and folate supplementation (although we did not consider the folate dose). We also

Table 3 Rates of intrauterine death (events) by different AED treatments

				Exact 95% CLs, %		
AED dose range, mg/d	Events	Sample	Rate, %	Lower	Upper	*p* Value[a]
Lamotrigine						0.2308
≤180	31	527	5.9	4.0	8.3	
>180 to ≤325	85	946	9.0	7.2	11.0	
>325	34	437	7.8	5.5	10.7	
Overall	150	1,910	7.9	6.7	9.2	
Carbamazepine						0.305
≤450	52	63.1	8.2	6.2	10.7	
>450 to ≤700	32	480	6.7	4.6	9.3	
>700	60	602	10.0	7.7	12.6	
Overall	144	1,713	8.4	7.1	9.8	
Valproic acid						0.4660
≤750	47	572	8.2	6.1	10.8	
>750 to ≤1,200	33	483	6.8	4.8	9.5	
>1,200	15	116	12.9	7.4	20.4	
Overall	95	1,171	8.1	6.6	9.8	
Levetiracetam						
Overall	28	324	8.6	5.8	12.3	
Oxcarbazepine						
Overall	22	262	8.4	5.3	12.4	
Phenobarbital						
Overall	22	260	8.5	5.4	12.5	
Polytherapy						
Overall	171	1,415	12.1	10.4	13.9	

Abbreviations: AED = antiepileptic drug; CL = confidence limit.
[a] Cochran-Armitage trend test for testing a linear dose-response relationship across the dose-range categories. Sample sizes were not large enough to test for dose effects in levetiracetam, oxcarbazepine, and phenobarbital.

Table 4 Results of multivariable random-effects log-binomial analysis

Parameter	RR	95% CL Lower	95% CL Upper	p Value
Lamotrigine vs valproic acid	0.851	0.658	1.101	0.220
Carbamazepine vs valproic acid	0.904	0.688	1.189	0.472
Levetiracetam vs valproic acid	0.888	0.589	1.337	0.569
Oxcarbazepine vs valproic acid	0.804	0.505	1.280	0.358
Phenobarbital vs valproic acid	0.839	0.531	1.326	0.452
Polytherapy vs monotherapy	1.376	1.137	1.665	0.001
Localization-related epilepsy vs idiopathic generalized[a]	1.130	0.937	1.361	0.201
Undetermined/unclassifiable vs idiopathic generalized[a]	1.288	1.000	1.662	0.050
Folic acid (exposed vs not exposed)	0.946	0.809	1.105	0.482
Gestational week at recruitment	0.840	0.816	0.865	<0.0001
Maternal age	1.056	1.039	1.072	<0.0001
Family history of epilepsy (yes vs no)	1.019	0.622	1.667	0.942
Father educational level	0.838	0.669	1.051	0.126
Mother educational level	0.811	0.642	1.023	0.077
Major seizure first trimester (yes vs no)	1.013	0.783	1.311	0.921
No. previous intrauterine deaths	1.092	1.002	1.191	0.045
Parity				
1 vs 0	0.921	0.779	1.090	0.338
≥2 vs 0	0.809	0.601	1.087	0.159
Parental MCM (yes vs no)	1.919	1.199	3.072	0.007

Abbreviations: CL = confidence limit; MCM = major congenital malformation; RR = risk ratio.
[a] Localization-related is equivalent to focal, and idiopathic generalized in most cases is equivalent to genetic generalized epilepsy in the new terminology.[12]

have more precise information about AED use, including timing and doses, rather than using filled prescriptions as an estimate of the drug exposure, and we were able to make a distinction between mono- and polytherapy, which turned out to be important. Admittedly, we did not have access to AED serum concentrations for a more precise estimation of drug exposure. This was not considered feasible in a large-scale multinational pregnancy registry. Furthermore, there is no consensus on what the optimal use of serum concentrations might be to assess fetal exposure of relevance for intrauterine deaths: unbound or total concentrations, peak or trough concentrations, and when during pregnancy?

The fact that in our analysis the strongest predictor of intrauterine death was the presence of MCMs in the mother or father suggests that fetal loss is related more to intrinsic and possibly genetic parental or maternal transplacental factors than to epilepsy or its treatment. Five of these pregnancies involved maternal MCMs of the uterus, which is an established risk factor for miscarriage in the general population.[17] Our observation that women with undetermined or unclassified epilepsy were at increased risk of pregnancy loss has no clear explanation, although the possibility exists that inability to classify the epilepsy reflected a poorer quality of care in general that might affect pregnancy outcomes. A previous study of 1,587 pregnancies among 582 women with epilepsy evaluated by telephone survey and review of medical records in the United States reported higher rates of spontaneous abortions among women with localization-related epilepsy,[18] a finding that we could not confirm.

We found that folate supplementation had no identifiable effect on the rate of intrauterine death: this is in contrast with the finding of an earlier small study comprising 388 retrospective as well as prospective pregnancies of women with epilepsy, in whom periconceptional folate was found to reduce the rate of spontaneous abortions.[19] The latter study, however, did not have the power to control for other risk factors. A limitation of our analysis, on the other hand, is the classification of appropriate folate supplementation, which we defined arbitrarily only by exposure time (started at least 3 months before conception and maintained throughout the first trimester irrespective of dose), but similar definitions have been used by others.[20]

Our study has strengths but also limitations. Strengths include the prospective design, the systematic collection of information on many potential risk factors, and the unparalleled size of the cohort. A further strength is that the same database has been used to analyze other outcomes including MCM rates and seizure control in relation to different AED treatments. Limitations include the observational (nonrandomized) nature of the study, the lack of a control group of healthy women or untreated women with epilepsy (a drawback of modest relevance, because the main objective of EURAP is to compare outcomes in relation to different treatments among women with epilepsy that need to be treated during pregnancy), and the fact that early spontaneous abortions could not be identified with a median time of enrollment in the study at gestational week 8, implying that potential differences in rates of early intrauterine death across treatments cannot be excluded.

The present analysis indicates that the risk of intrauterine death in pregnancies of women with treated epilepsy is strongly predicted by the presence of parental MCMs and, to a lesser extent, by the number of previous pregnancies resulting in intrauterine deaths. Other risk factors, such as stage of gestation and maternal age, appear to be similar to those previously identified in the general population. Of note, the risk of intrauterine death does not appear to be influenced by occurrence of seizures in early

pregnancy or by the type of AED used in monotherapy, despite the fact that major differences in rates of MCMs in relation to AED type and dosage had been documented in the same cohort. The only identified treatment-related factor affecting the risk of intrauterine death was AED polytherapy, which is best avoided to also reduce other teratogenic risks.[2,3]

AUTHOR CONTRIBUTIONS

All authors contributed equally to the design of the study. E.B. conducted the statistical analysis. All authors contributed equally to the interpretation of the data. T.T. and D.B. drafted the first version of the manuscript, and all authors contributed equally to input to the first draft and the finalization of the submitted manuscript.

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Comment: Stillbirths and spontaneous abortions in women with epilepsy on AEDs

Our knowledge about the association between antiepileptic drugs (AEDs) and major congenital malformations (MCMs) or neurodevelopmental outcomes has increased greatly in the past decade. Yet our understanding regarding the occurrence of other important outcomes, such as stillbirths or spontaneous abortions in women with epilepsy, is limited.

In this issue of *Neurology*®, Tomson et al.[1] discuss the results of the largest observational study of its kind, examining the risk of intrauterine death in 7,055 pregnant women with epilepsy on AEDs. The risk did not differ across AED monotherapies. Conversely, maternal age, parental history of MCMs, AED polytherapy, and number of prior intrauterine deaths were associated with a higher risk.

This important and well-conducted study has many strengths, most notably the very large sample size and the breadth of potential confounders captured prospectively; however, there are some limitations, such as the lack of information on AED levels or epilepsy severity, and the exclusion of data regarding early pregnancy. It is surprising that folate was not associated with a lower risk of intrauterine death, since recent studies suggest it is associated with better outcomes (e.g., higher IQs).[2] However, the authors did not evaluate outcomes related to folate dose because of the challenge of considering time and duration of exposure as additional dimensions. Finally, differences across polytherapies were not evaluated given the multitude of possible combinations.

The authors are to be congratulated for conceptualizing this clinically vital study. It provides important information that can be used in counseling women with epilepsy. Genetic consultation should be considered in those with a parental history of MCMs or prior intrauterine deaths in an attempt to optimize future pregnancy outcomes in this population. Finally, physicians should aim to control seizures with AED monotherapy when feasible to minimize this substantial risk.

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Nathalie Jetté, MD, MSc

From the Department of Clinical Neurosciences and Hotchkiss Brain Institute, and Department of Community Health Sciences and O'Brien Institute for Public Health, University of Calgary, Canada.

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DISCLOSURE

T. Tomson is a full-time employee of Karolinska Institutet, he has been associate editor of *Epilepsia* and is currently the same for *Epileptic Disorders*, has received speakers honoraria for his institution from Eisai, UCB, and Actavis, honoraria for his institution for advisory boards from UCB and Eisai, and received research support from Stockholm County Council, CURE, GSK, UCB, Eisai, Bial, and Novartis. D. Battino has received speakers fees from UCB Pharma. E. Bonizzoni has received consultancy fees from Italfarmaco, Zambon, Polichem, Roche, and Sanofi-Aventis. J. Craig received research grants and speakers fees from UCB Pharma, Eisai, GSK, Sanofi-Aventis, Pfizer, and Janssen-Cilag. D. Lindhout received research grants from Janssen-Cilag, GSK, Pfizer, and Netherlands Epilepsy Foundation. E. Perucca received research funds from the European Union, the Italian Ministry of Health, the Italian Ministry for Education and University, and the Italian Medicines Agency. He also received speakers or consultancy fees and/or research grants from Eisai, GSK, UCB Pharma, and ViroPharma and has been on advisory boards of Eisai, GW Pharma, and ViroPharma. A. Sabers received consultancy or lecture fees and is on advisory boards for Eisai Denmark and UCB Nordic and has received travel support from Eisai Denmark, GSK, and UCB Nordic. S. Thomas and F. Vajda report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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