



EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report

May 2008

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BACKGROUND

All old-generation antiepileptic drugs (AEDs) are considered to be teratogenic and AEDs are among the most common causes of adverse effects to the foetus. The risks associated with the treatment of epilepsy during pregnancy is therefore of major concern to all women of childbearing potential with epilepsy. The information on the comparative teratogenicity of these AEDs in humans is, however, conflicting, mainly due to inadequate sample size and methodological differences between previous studies. The teratogenic potential of newer AEDs is even less known, a situation that prevents a rational approach to AED treatment in women of childbearing potential.

To address this problem, it is necessary to compile more information on outcome of pregnancies following maternal exposure to AEDs. Such information is needed to provide pre-pregnancy counselling concerning teratogenic risks, and possibilities for specific prenatal monitoring, including prenatal diagnosis of foetal disorders associated with specific medications. Given the current number of available AEDs and combinations, very large numbers of pregnancies have to be evaluated in order to establish the safety of each regimen. Large denominators are also needed because of the qualitative diversity of the main endpoint of outcome, major congenital malformations.

A number of independent groups with experience and interest in maternal and foetal well-being in association with maternal AED use have agreed on a prospective international multi-centre study of pregnancies with AEDs. Data from all participating groups are shared in a Central Registry of Antiepileptic Drugs and Pregnancy (EURAP). EURAP was established in the first centres in some European countries and has since then gradually expanded to include more centres and countries now involving also Asia, Oceania and Latin America.

OBJECTIVE OF EURAP

The primary objective of EURAP is to evaluate and determine the comparative risk of major foetal malformations following intake of AEDs (old and new) and their combinations during pregnancy.

METHODS

EURAP is a prospective and retrospective observational study. Women taking AEDs at the time of conception, irrespective of the indication, may be included. To avoid selection bias, only pregnancies recorded before foetal outcome is known and within week 16 of gestation are included in the prospective risk assessment. Cases ascertained later in pregnancy are recorded as retrospective cases, as they may provide signals, but are not included in the comparative risk evaluation.

Information on patient's demographics, type of epilepsy, seizure frequency, family history of malformations, drug therapy and of other potential risk factors is obtained, and follow-up data are collected once at each trimester, at birth and at one year after delivery.

Networks of reporting physicians have been established in countries taking part in the collaboration. During the course of the pregnancy, and the follow-up time after delivery, the participating physician enters data into five Subforms (Subforms A-E) for each patient.

Subform A is completed on enrolment of the patient, Subform B after the first trimester, Subform C after the second trimester, Subform D within three months after delivery, and Subform E within 14 months after birth. Immediately after completion, each Subform is submitted to the national coordinator for review. The

national coordinator transfers the reviewed and accepted Subform to the Central EURAP Registry in Milan, Italy.

EVALUATION OF OUTCOME

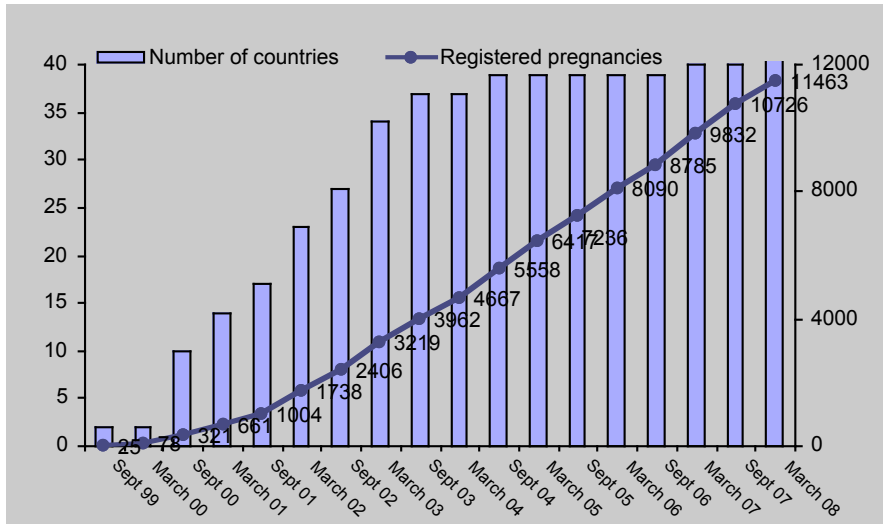
The physician records descriptively abnormalities observed in the offspring. The final assessment and classification of the type of malformation is the responsibility of the Central Project Commission (CPC). In order to facilitate a uniform and objective assessment, reports of malformations are assessed regularly by an outcome assessment committee, which is kept blinded with respect to the type of exposure.

Outcome in relation to exposure to individual drugs or drug combinations will be assessed only after sufficient data is available for a meaningful statistical analysis. Determination of the sample size needed is complicated by lack of reliable information about the distribution of individual drugs and their combinations and about the prevalence of the teratogenic event. Applying the general empirical rule that the ratio between the overall number of events (teratogenic events) and the number of explanatory variables (predictors) should be at least equal to 10, a total sample size of at least 5,000 prospectively ascertained pregnancies would be needed to allow analysis of 25 predictors (different AEDs and other relevant risk factors) assuming a prevalence of malformations in the order of 5%.

INTERIM REPORT

EURAP was implemented in the first two countries in Europe in 1999 and has since then grown rapidly with increasing numbers of participating countries from Europe, Australia, Asia and South America. This development is also reflected by increasing numbers of enrolled pregnancies. The development since 1999 is illustrated in Fig. 1.

Fig 1 Number of participating countries and pregnancies reported to the Central Registry by May 2008.



The present report is based on data available in the Central Registry by May 6, 2008. At that time more than 750 reporting physicians from 42 countries had contributed cases to the Central Registry. Countries that had been active are listed in Table 1.

Table 1
Countries that have contributed with pregnancies reported to the Central Registry of EURAP

- Albania
- Argentina
- Australia
- Austria
- Belgium
- Belarus
- Chile
- China
- Croatia
- Czech Republic
- Denmark
- Emirates
- Finland
- France
- Georgia
- Germany
- Guatemala
- Hong Kong
- Hungary
- India
- Israel
- Italy
- Japan
- Lithuania
- Macedonia
- The Netherlands
- Norway

Philippines
Poland
Portugal
Russia
Scotland
Serbia and Montenegro
Slovakia
Slovenia
Spain
Sweden
Switzerland
Taiwan
Turkey
Ukraine
United Kingdom

By the cut-off date for this report (6 May 2008), 11,628 pregnancies had been entered into the central database. Of these, 2,502 were retrospective, a further 1,308 are excluded for reasons specified below (point 1 and 2), 988 are pending (awaiting updates or corrections of different sub-forms), 1,208 are ongoing pregnancies and 5,292 are prospective which have completed the study including the one-year follow-up after birth. Reasons for not including pregnancies in the present interim report were:

1. Pregnancies that failed to meet inclusion criteria (n=47).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n=1,261).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n=988).
4. Ongoing pregnancies, updated and corrected (n=1,208).
5. Retrospective, but completed and corrected (n=2,014).
6. Retrospective, i.e. initially classified as prospective pregnancies but finally accepted as retrospective cases because one or more CRF subforms were submitted after the set deadlines (n=150).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=14). This includes fetal loss with unknown fetal status (n=3), induced abortion with insufficient information on fetus (n=2), and anomalies in livebirths where the information was insufficient to determine if qualifying for malformation diagnosis (in most cases abdominal hernias).
8. Pregnancies completed by the cut-off date, but too recent (after April 9, 2008) for having their classification of outcome completed in time for this report (n=235).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=419).

Thus in total 5,292 prospective pregnancies (enrolled at the latest during the 16th gestational week) are included in this report. Seventy-six of these pregnancies (1.4%), that otherwise met our criteria for prospective pregnancies, had an ultrasound examination performed before enrolment.

The classification of the epilepsy among the prospective pregnancies is given in table 2. Epilepsy was the indication for treatment in all but 50 (1%) of the pregnant women.

Table 2

Classification of the epilepsy in 5,292 prospective pregnancies.

Epilepsy	N	%
Generalized	2,212	41.8
Localisation-related	2,754	52.0
Undetermined	184	3.5
Missing information	92	1.7
No epilepsy	50	1.0
Total	5,292	100.0

The maternal age among prospective cases was 29.6±5.1 years (mean±SD), ranging from 14 to 45 years. The women were of Caucasian ethnicity in 89.6% and of Asian in 6.6%.

The number of the current pregnancy in individual women is presented in Table 3.

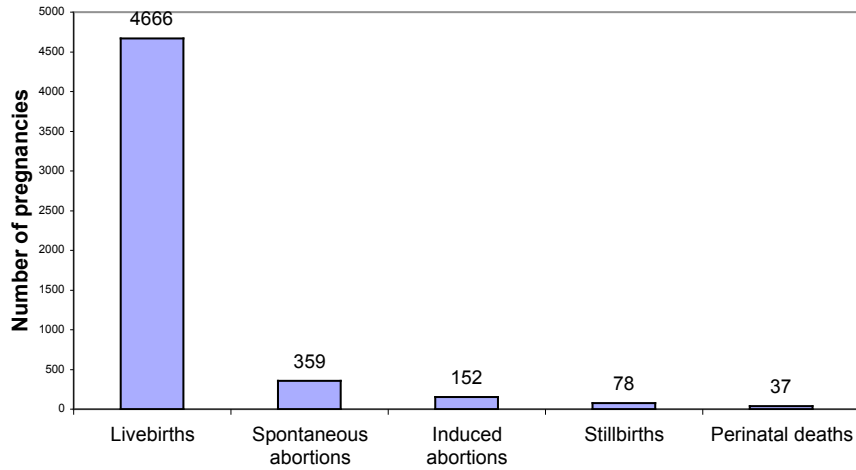
Table 3

Number of the pregnancy in prospective cases

Gravida	N	%
1st pregnancy	2,432	45.9
2nd pregnancy	1,606	30.4
3rd pregnancy	725	13.7
4th pregnancy	311	5.9
5th pregnancy	132	2.5
> 5th pregnancy	86	1.6
Total	5,292	100.0

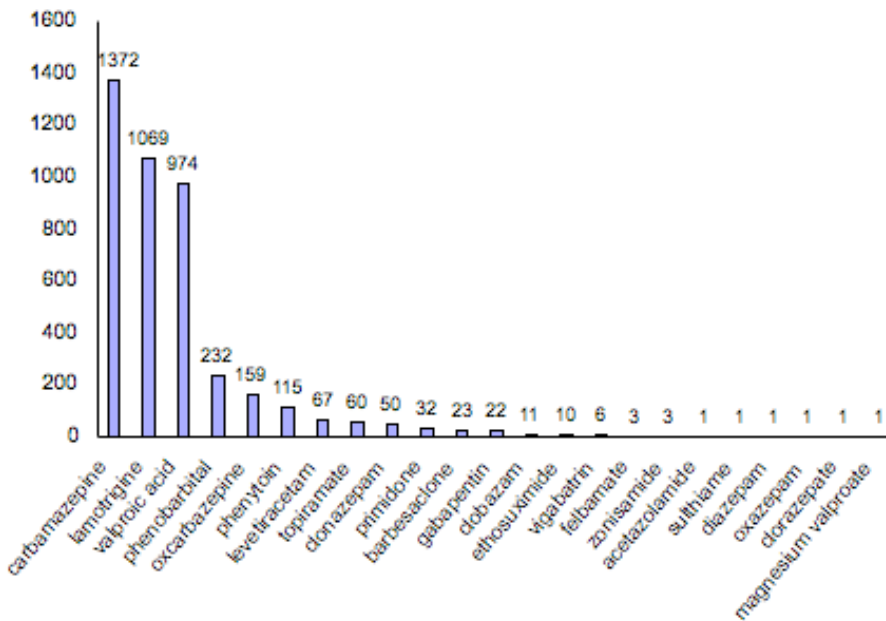
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the 152 induced abortions, 33 were for fetal indication (major malformation or other abnormalities detected by prenatal screening).

Figure 2
Outcome of prospective pregnancies.



Of the pregnancies, 4214 (80.5%) involved women on a single AED, 872 (16.6%) were on two AEDs whereas 151 (2.9%) took three AEDs or more. Fifty-five women (1.0%) were not on AED treatment during the 1st trimester. The exposure to the different AEDs in monotherapy among the prospective pregnancies is presented in Figure 3.

Figure 3
Number of prospective pregnancies with exposure to different AEDs in monotherapy



There were 179 different AED combinations. The most frequently used combinations were lamotrigine and valproic acid (n=135), carbamazepine and lamotrigine (n=75), carbamazepine and phenobarbital (n=52) and carbamazepine and valproic acid (n=51) (Table 4).

Table 4.
The most common AED combinations

lamotrigine + valproic acid	135
carbamazepine + lamotrigine	75
carbamazepine + phenobarbital	52
carbamazepine + valproic acid	51
lamotrigine + levetiracetam	39
carbamazepine + levetiracetam	32
carbamazepine + topiramate	28
phenobarbital + valproic acid	26
lamotrigine + topiramate	26
carbamazepine + clobazam	24
clonazepam + valproic acid	23
carbamazepine + clonazepam	20
lamotrigine + phenobarbital	17
lamotrigine + clonazepam	17
phenobarbital + phenytoin	17

The number of pregnancies with exposure to different new generation AEDs taken in combination with other AEDs are listed in Table 5.

Table 5
Number of pregnancies with different new generation AEDs in combination therapy

AED	N
Lamotrigine	449
Topiramate	137
Levetiracetam	128
Oxcarbazepine	73
Gabapentin	39
Vigabatrin	32
Tiagabine	7
Zonisamide	5
Pregabalin	2

TERATOGENIC OUTCOME

There were 280 major congenital malformations (MCM) and 47 chromosomal (CHR)/monogenic abnormalities in the prospective cohort of 4,933 pregnancies (spontaneous abortions excluded) as shown in Table 6.

Table 6

Outcome	Outcome classification	N
MCM	Multiple major	24
	Isolated major	254
	Association*	1
	Sequence‡	1
		280
CHR or monogenic	CHR	36
	Monogenic	11
		47
Total		327

*idiopathic pattern of multiple anomalies arising during blastogenesis.

‡pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor

In this report we will confine our analysis to the 280 MCM including 28 induced abortions, five stillbirths and eight neonatal deaths. Of the 239 live births, 22 cases of malformations were ascertained prenatally, 130 were first reported at birth and 87 within one year after birth.

Among the 280 cases with MCM, 53 were detected by ultrasound examination. Out of these 53, there were 27 induced abortions, 4 stillbirths and 22 live births.

The 280 cases represent a malformation rate of 5.7% of all prospective pregnancies for which follow-up has been completed (280/4,933), and the same rate of 5.7% is obtained if the 68 cases with ultrasound before enrolment are excluded (276/4,865). The type of malformations is described in Table 7.

Table 7

MCM	APPARATUS / ICD-9-CM coding	MCM	CHR or monogenic
	Nervous system		
	740 Anencephalus and similar anomalies	3	0
	741 Spina bifida	24	0
	742 Other congenital anomalies of nervous system	6	2
	Eye		
	743 Congenital anomalies of eye	4	1
	Congenital heart disease		
	745 Bulbus cordis anomalies and anomalies of cardiac septal closure	47	4
	746 Other congenital anomalies of heart	6	0
	747 Other congenital anomalies of circulatory system	8	2
	748 Congenital anomalies of respiratory system	1	0
	Oro facial clefts		
	749 Cleft palate and cleft lip	16	0
	Digestive system		
	751 Other congenital anomalies of digestive system	5	0
	Genital		
	752 Congenital anomalies of genital organs	38	1
	Urinary		
	753 Congenital anomalies of urinary system	19	0
	Limbs		
	755 Other congenital anomalies of limbs	2	0
	755.0 Polydactyly	1	0
	Musculo-skeletal deformities		
	754 Certain congenital musculoskeletal deformities	23	1
	Other musculo-skeletal anomalies		
	756 Other congenital musculoskeletal anomalies	4	2
	756.0 Anomalies of skull and face bones	5	0
	756.6 Anomalies of diaphragm	4	0
	Skin		
	757 Congenital anomalies of the integument	0	1
	Other and unspecified congenital anomalies		
	759 Other and unspecified congenital anomalies	0	4
	Association	1	0
	Multiple Major	24	
	Sequence	1	
	Chromosomal anomalies		
	758 Chromosomal anomalies	0	26
	Outside malformation chapter codes		
	210-229 Benign neoplasm*	3	1
	550-553 Hernia of abdominal cavity	35	0
	270 Disorders of amino-acid transport and metabolism**	0	1
	320-389 Diseases of the nervous system and sense organs	0	1
	Total	280	47

*Haemangiomas

**Albinism

In 238 out of 3,949 pregnancies with AED monotherapy one or more birth defects were observed (6.0%), as opposed to 87 out of 932 pregnancies with AED polytherapy (9.3%) as shown in Table 8.

Table 8

	Monotherapy		Polytherapy	
	N	%	N	%
MCM	198	5.0	80	8.6
CHR or monogenic	40	1.0	7	0.7
No malformation	3,711	94.0	845	90.7
Total	3,949	100	932	100

Outcome in relation to exposure to individual drugs or specific drug combinations will not be assessed or reported until more pregnancies have been completed (c.f. Evaluation of outcome section above).

ORGANISATION, FUNDING AND SUPPORT

EURAP is a consortium of independent research groups working on a non-profit basis. The project is administratively organised by the Central Project Commission (CPC) with members representing different geographical areas and disciplines. The project has been supported by educational grants to the CPC from Eisai Pharmaceuticals, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Pfizer, Sanofi-Synthelabo, UCB Pharma and. In addition, national and regional networks may receive support from the same or other pharmaceutical companies.

APPENDIX

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