



EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report

November 2008

Central Study Coordinator

Dr Dina Battino
Fondazione I.R.C.C.S. Istituto Neurologico "Carlo Besta"
Via Celoria 11
20 133 Milano, Italy
Tel: + 39 (0)2 23 94 2230
Fax: + 39 (0)2 700 42 91 60
E-mail: dbattino@istituto-besta.it

Chairman Central Project Commission

Dr Torbjörn Tomson
Department of Neurology
Karolinska University Hospital
S-171 76 Stockholm
Sweden
Tel: + 46 (0)8 51773705
Fax: + 46 (0)8 51773757
E-mail: torbjorn.tomson@karolinska.se

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

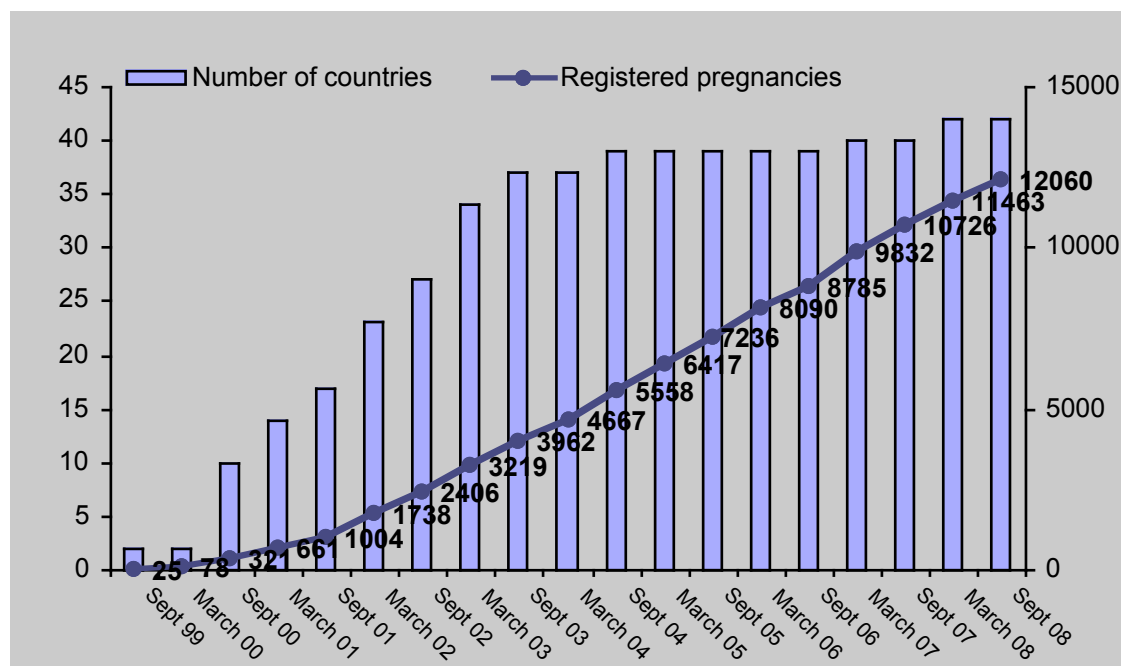
The physician records descriptively abnormalities observed in the offspring. The final assessment and classification of the type of malformation is the responsibility of the Central Project Commission (CPC). In order to facilitate a uniform and objective assessment, reports of malformations are assessed 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 November 2008.



The present report is based on data available in the Central Registry by November 17, 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 (17 November 2008), 12,386 pregnancies had been entered into the central database. Of these, 2,658 were retrospective, a further 1,390 are excluded for reasons specified below (point 1 and 2), 1052 are pending (awaiting updates or corrections of different sub-forms), 1125 are ongoing pregnancies and 5,623 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=51).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n=1,339).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n=1052).
4. Ongoing pregnancies, updated and corrected (n=1,125).
5. Retrospective, but completed and corrected (n=2,168).
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=177).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=13). This includes fetal loss with unknown fetal status (n=4), induced abortion with insufficient information on fetus (n=3), 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 september 9, 2008) for having their classification of outcome completed in time for this report (n=287).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=452).

Thus in total 5,623 prospective pregnancies (enrolled at the latest during the 16th gestational week) are included in this report. eighty-eight of these pregnancies (1.6%), 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 53 (1%) of the pregnant women.

Table 2

Classification of the epilepsy in 5,623 prospective pregnancies.

Epilepsy	N	%
Generalized	2,343	41.7
Localisation-related	2,942	52.3
Undetermined	192	3.4
Missing information	93	1.6
No epilepsy	53	1.0
Total	5,623	100.0

The maternal age among prospective cases was 29.6 ± 5.1 years (mean \pm SD), ranging from 14 to 46 years. The women were of Caucasian ethnicity in 89.5% and of Asian in 6.7%.

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

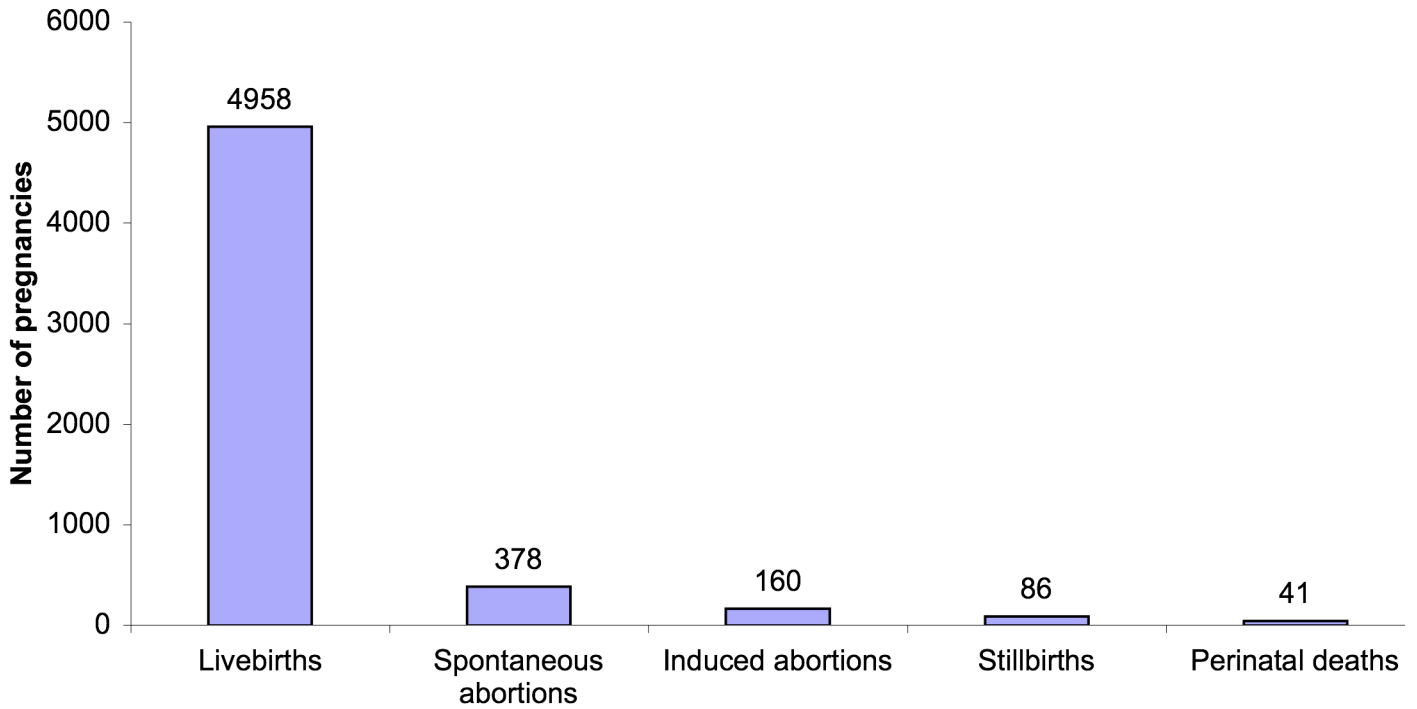
Table 3

Number of the pregnancy in prospective cases

Gravida	N	%
1st pregnancy	2,589	46.0
2nd pregnancy	1,706	30.3
3rd pregnancy	770	13.7
4th pregnancy	329	5.9
5th pregnancy	140	2.5
> 5th pregnancy	89	1.6
Total	5,623	100.0

The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the 160 induced abortions, 33 were for fetal indication (major malformation or other abnormalities detected by prenatal screening).

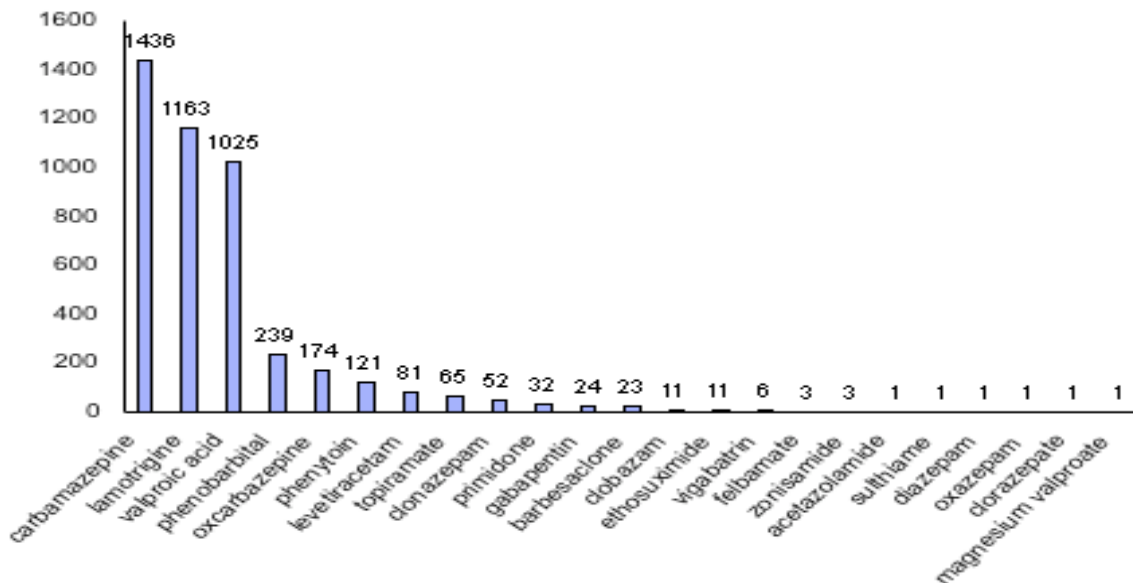
Figure 2. Outcome of prospective pregnancies



Of the pregnancies, 4475 (79.6%) involved women on a single AED, 927 (16.7%) were on two AEDs whereas 160 (2.9%) took three AEDs or more. sixty-one 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 182 different AED combinations. The most frequently used combinations were lamotrigine and valproic acid (n=140), carbamazepine and lamotrigine (n=79), carbamazepine and phenobarbital (n=54) and carbamazepine and valproic acid (n=51) (Table 4).

Table 4.
The most common AED combinations

lamotrigine + valproic acid	140
carbamazepine + lamotrigine	79
carbamazepine + phenobarbital	54
carbamazepine + valproic acid	51
lamotrigine + levetiracetam	44
carbamazepine + levetiracetam	34
carbamazepine + topiramate	30
lamotrigine + topiramate	30
phenobarbital + valproic acid	28
carbamazepine + clobazam	28
clonazepam + valproic acid	25
carbamazepine + clonazepam	21
lamotrigine + clonazepam	19
lamotrigine + phenobarbital	18
Clobazam + lamotrigine	18
lamotrigine + oxcarbazepine	18
phenobarbital + phenytoin	18

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	479
Topiramate	150
Levetiracetam	143
Oxcarbazepine	77
Gabapentin	41
Vigabatrin	32
Tiagabine	7
Zonisamide	6
Pregabalin	4

TERATOGENIC OUTCOME

There were 301 major congenital malformations (MCM) and 51 chromosomal (CHR)/monogenic abnormalities in the prospective cohort of 5,245 pregnancies (spontaneous abortions excluded) as shown in Table 6.

Table 6

Outcome	Outcome classification	N
MCM	Multiple major	26
	Isolated major	273
	Association*	1
	Sequence‡	1
		301
CHR or monogenic	CHR	40
	Monogenic	11
		51
Total		352

*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 301 MCM including 31 induced abortions, five stillbirths and nine neonatal deaths. Of the 256 live births, 23 cases of malformations were ascertained prenatally, 141 were first reported at birth and 92 within one year after birth.

Among the 301 cases with MCM, 56 were detected by ultrasound examination. Out of these 56, there were 30 induced abortions, 3 stillbirths and 23 live births.

The 301 cases represent a malformation rate of 5.7% of all prospective pregnancies for which follow-up has been completed (301/5,245), and the same rate of 5.7% is obtained if the 80 cases with ultrasound before enrolment are excluded (297/5,169). The type of malformations is described in Table 7.

Table 7

	MCM	CHR or monogenic
APPARATUS / ICD-9-CM coding		
Nervous system		
740 Anencephalus and similar anomalies	3	0
741 Spina bifida	26	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	50	4
746 Other congenital anomalies of heart	9	0
747 Other congenital anomalies of circulatory system	8	2
748 Congenital anomalies of respiratory system	2	0
Oro facial clefts		
749 Cleft palate and cleft lip	17	0
Digestive system		
751 Other congenital anomalies of digestive system	7	0
Abdominal wall defects		
Genital		
752 Congenital anomalies of genital organs	41	1
Urinary		
753 Congenital anomalies of urinary system	19	0
Limbs		
755 Other congenital anomalies of limbs	3	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 Sequence	26	
Chromosomal anomalies	1	
758 Chromosomal anomalies	0	30
Outside malformation chapter codes		
210-229 Benign neoplasm*	3	1
550-553 Hernia of abdominal cavity	38	0
270 Disorders of amino-acid transport and metabolism**	0	1
320-389 Diseases of the nervous system and sense organs	0	1
Total	301	51

*Haemangiomas

**Albinism

In 258 out of 4,197 pregnancies with AED monotherapy one or more birth defects were observed (6.0%), as opposed to 92 out of 992 pregnancies with AED polytherapy (9.3%) as shown in Table 8.

Table 8

	Monotherapy		Polytherapy	
	N	%	N	%
MCM	217	5.2	82	8.3
CHR or monogenic	41	1.0	10	1.0
No malformation	3,939	93.8	900	90.7
Total	4,197	100	992	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

Central Project Commission

Dina Battino, Milano
Erminio Bonizzoni, Pavia
John Craig, Belfast
Dick Lindhout, Utrecht
Emilio Perucca, Pavia
Anne Sabers, Copenhagen
Torbjörn Tomson, Stockholm, (chair)
Frank Vajda, Melbourne

Central Study Coordinator

Dina Battino, Milan

Scientific Advisory Board

Bernd Schmidt, Freiburg
Martin J Brodie, Glasgow

Outcome Assessment Committee

Richard Finnell, Houston, Texas
Francesca Faravelli, Genoa, Italy
Elisabeth Robert-Gnansia, Lyon, France

National/Regional Coordinators

Silvia Kochen, Argentina

Frank Vajda, Australia

Gerhard Luef, Austria

Dick Lindhout and **Klara Flipsen-ten Berg**, Benelux

Alejandro de Marinis, Chile

Dinko Vitezic, Croatia

Jana Zarubova and **Robert Kuba**, Czech Republic

Anne Sabers, Denmark

Reetta Kälviäinen, Finland

Otar Toidze and **Sofia Kasradze**, Georgia

Bettina Schmitz, Germany

Patrick Kwan, Hong Kong

Gábor Barcs, Hungary

Sanjeev V Thomas, India

Miri Neufeld, Israel

Aldo Paggi and **Daniela Mamoli**, Italy

Hideyuki Ohtani, Japan

Ruta Mameniskiene, Lithuania

Gordana Kiteva-Trencevska, Macedonia

Karl-Otto Nakken, Norway

Weiping Liao, People's Republic of China

Leonor Cabral-Lim, Philippines

Joanna Jedrzejczak, Poland

Alla Guekht and **Oksana Lokshina**, Russia

Aline Russell, Scotland

Dragoslav Sokic, Serbia and Montenegro

Vladimir Safcak, Slovakia

Bostjan Cebular, Slovenia

Meritxell Martinez Ferri, Spain

Torbjörn Tomson, Sweden

Barbara Tettenborn and Heike Juch, Switzerland

Chi-Wan Lai, Taiwan

Çigdem Özkara, Turkey

John Craig, UK and Ireland