



EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report

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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

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

EVALUATION OF OUTCOME

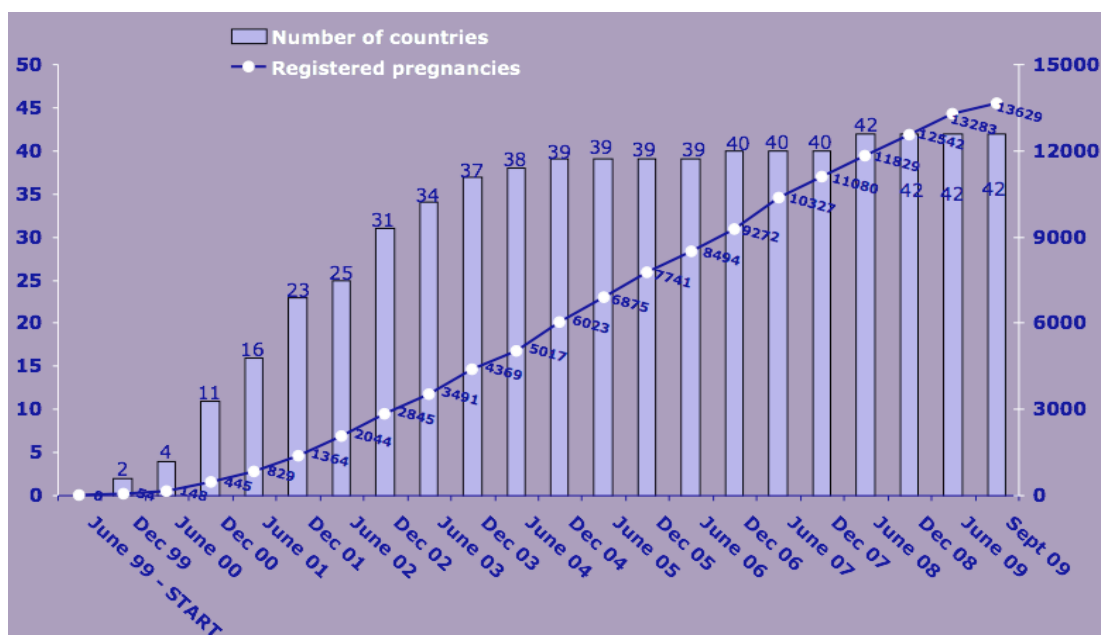
The physician records descriptively abnormalities observed in the offspring. The final assessment and classification of the type of malformation is the responsibility of the Central Project Commission (CPC). In order to facilitate a uniform and objective assessment, reports of malformations are assessed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

The analysis of outcome in relation to exposure to individual drugs has been initiated but the results will be included in the EURAP Interim Reports only after completion of peer review.

INTERIM REPORT

EURAP was implemented in the first two countries in Europe in 1999 and has since then grown rapidly with countries participating from Europe, Australia, Asia and South America. This development is 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 September 2009



The present report is based on data available in the Central Registry by September 30, 2009. 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 (n=42)

- 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 (30 September 2009), 13,629 pregnancies had been entered into the central database. Of these, 2,901 were retrospective, a further 1,512 are excluded for reasons specified below (point 1 and 2), 1355 are pending (awaiting updates or corrections of different sub-forms), 925 are ongoing pregnancies and 6,668 are prospective which have completed the study including, when relevant, 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=55).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n=1,457).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n=1,355).
4. Ongoing pregnancies, updated and corrected (n=925).
5. Retrospective, but completed and corrected (n=2,386).
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=219).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=22). This includes 1 stillbirth with unknown fetal status, induced abortion with insufficient information on fetus (n=5), and anomalies in livebirths where the information was insufficient to determine if qualifying for malformation diagnosis (n=16).
8. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=542).

Thus in total 6,668 prospective pregnancies (enrolled at the latest during the 16th gestational week) are included in this report. One hundred and nine 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 59 (1%) of the pregnant women.

Table 2. Classification of the epilepsy in 6,668 prospective pregnancies.

Epilepsy	N	%
Generalized	2,765	41.5
Localisation-related	3,494	52.4
Undetermined	231	3.4
Missing information	119	1.8
No epilepsy	59	0.9
Total	6,668	100.0

The maternal age among prospective cases was 29.6±5.1 years (mean±SD), ranging from 14 to 46 years.

The women were of Caucasian ethnicity in 89.3% and of Asian in 6.9%.

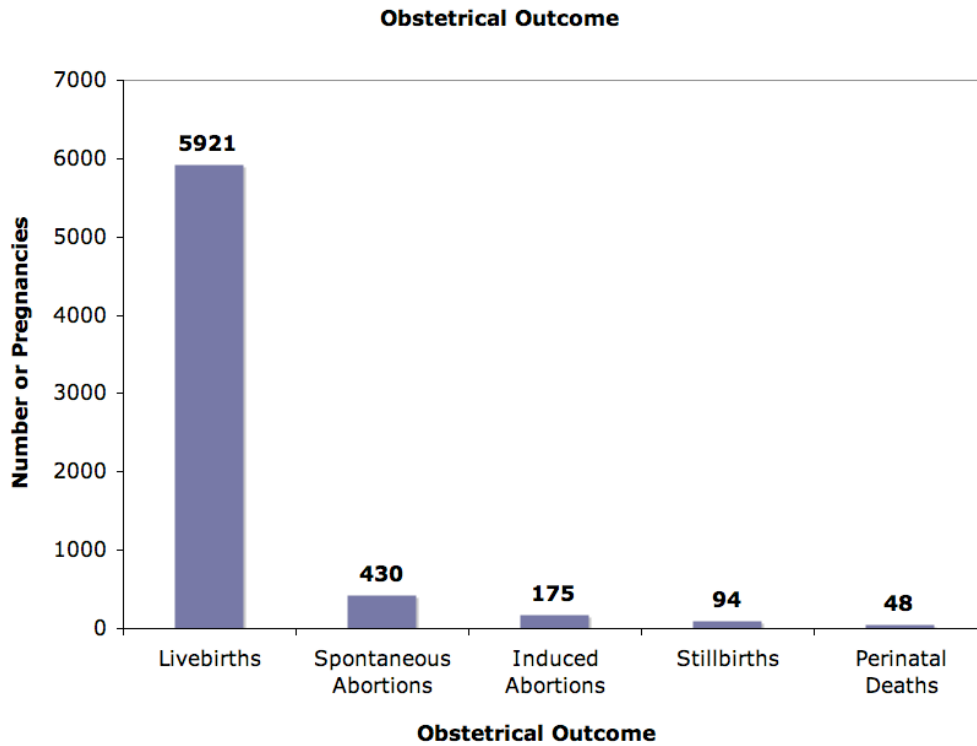
The number of the current pregnancy in individual women is presented in Table 3.

Table 3. Number of the pregnancy in prospective cases

Gravida	N	%
1st pregnancy	3,080	46.2
2nd pregnancy	2,009	30.1
3rd pregnancy	920	13.8
4th pregnancy	389	5.8
5th pregnancy	161	2.4
> 5th pregnancy	108	1.6
Not ascertained	1	0.0
Total	6,668	100.0

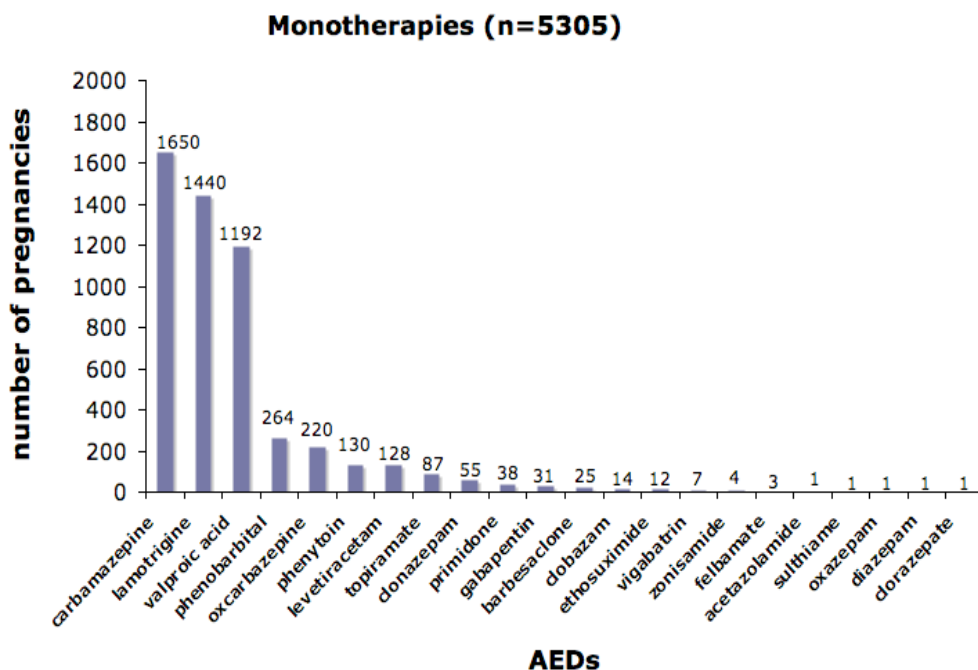
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the 175 induced abortions, 44 were for fetal indication (major malformation or other abnormalities detected by prenatal screening) and 20 for chromosomal abnormalities.

Figure 2. Obstetric Outcome of prospective pregnancies



Of the pregnancies, 5,305 (79.6%) involved women on a single AED, 1,089(16.3%) were on two AEDs whereas 192 (2.9%) took three AEDs or more. Eighty-two women (1.2%) 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 198 different AED combinations. The most frequently used combinations were lamotrigine and valproic acid (n=160), carbamazepine and lamotrigine (n=87), carbamazepine and valproic acid (n=61) and carbamazepine and phenobarbital (n=61) (Table 4).

Table 4. The most common AED combinations

lamotrigine + valproic acid	160
carbamazepine + lamotrigine	87
carbamazepine + valproic acid	61
carbamazepine + phenobarbital	61
lamotrigine + levetiracetam	56
carbamazepine + levetiracetam	52
lamotrigine + topiramate	39
carbamazepine + clobazam	33
carbamazepine + topiramate	33
phenobarbital + valproic acid	29
clonazepam + valproic acid	28
topiramate + valproic acid	23
carbamazepine + clonazepam	22
lamotrigine + clonazepam	22
clobazam + lamotrigine	22
lamotrigine + oxcarbazepine	21
lamotrigine + phenobarbital	19
phenobarbital + phenytoin	19

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	559
Levetiracetam	200
Topiramate	184
Oxcarbazepine	98
Gabapentin	46
Vigabatrin	33
Zonisamide	12
Tiagabine	7
Pregabalin	5

TERATOGENIC OUTCOME

There were 357 major congenital malformations (MCM), 5 syndromic cases and 38 chromosomal abnormalities in the prospective cohort of 6,238 pregnancies (spontaneous abortions excluded) as shown in Table 6.

Table 6. Pathological outcomes

Outcome	Outcome classification	N
MCM	Multiple major	33
	Isolated major	324
		357
SYNDROMES		5
CHR		38
Total		400

The 5 syndromic cases are 2 Marfan syndrome, 1 Incontinentia pigmenti, 1 Noonan syndrome and 1 Oculo-auriculo-vertebral syndrome.

In this report we will confine our analysis to the 357 MCM including 38 induced abortions, five stillbirths and thirteen neonatal deaths. Of the 301 live births, 27 cases of malformations were ascertained prenatally, 192 were first reported at birth and 81 within one year after birth.

Among the 357 cases with MCM, 68 were detected by ultrasound examination. Out of these 68, there were 34 induced abortions, 4 stillbirths, 3 perinatal deaths and 27 live births.

The 357 cases represent a malformation rate of 5.7% of all prospective pregnancies for which follow-up has been completed (357/6,238) and the same rate of 5.7% is obtained if the 101 cases with ultrasound before enrolment are excluded (352/6,137). The type of malformations is described in Table 7.

Table7

PATHOLOGICAL OUTCOME	DESCRIPTION	N
MCM	Multiple major	33
	Nervous system	
MCM	Spina Bifida	27
MCM	Anencephalus and similar	3
MCM	Hydrocephaly	5
MCM	Microcephaly	1
MCM	Nervous system (other malformations)	7
	all	43
	Heart	
MCM	Atrial septal defect	23
MCM	Ventricular septal defect	29
MCM	Congenital heart disease	23
MCM	Tetralogy of Fallot	5
MCM	Transposition of great vessels (complete)	2
MCM	Pulmonary valve stenosis	5
MCM	Hypoplastic left heart	5
	all	92
	Urinary system	
MCM	Urinary system (other malformations)	23
MCM	Renal Dysplasia	2
	all	25
	Digestive system	
MCM	Diaphragmatic hernia	5
MCM	Ano-rectal atresia and stenosis	1
MCM	Digestive system (other malformations)	5
MCM	Duodenal atresia or stenosis	1
MCM	Gastroschisis	1
	all	13
	Limbs	
MCM	Upper limb reduction	3
MCM	Syndactyly	5
MCM	Polydactyly	14
MCM	Club foot - talipes equinovarus	6
	all	28
	Musculoskeletal	
MCM	Musculo-skeletal (other malformations)	8
MCM	Hip dislocation and/or dysplasia	31
	all	39
	Genital system	
MCM	Genital (other malformations)	1
MCM	Hypospadias	41
	all	42
	Eye, ear, face and neck	
MCM	Congenital cataract	4
MCM	Congenital glaucoma	1
MCM	Ear, face and neck	2
MCM	Eye (other malformations)	1
	all	8
	Oro facial clefts	
MCM	Cleft lip with or without palate	9
MCM	Cleft palate	10
	all	19
	Other malformations (including sacral teratoma, cystic hygroma, haemangliomas, genetic syndromes & microdeletions)	
MCM		15
MCM	all	357
	Chromosomal	
CHR	Chromosomal	6
CHR	Down's syndrome	21
CHR	Edward syndrome/trisomy 18	4
CHR	Indeterminate sex	1
CHR	Klinefelter's syndrome	1
CHR	Patau syndrome/trisomy 13	2
CHR	Turner's syndrome	2
CHR	Wolff-Hirschorn syndrome	1
CHR	all	38
	Syndromes	
Syndrome	Marfan syndrome	2
Syndrome	Incontinentia pigmenti	1
Syndrome	Noonan's syndrome	1
Syndrome	Oculo-auriculo-vertebral syndrome	1
Syndrome	all	5
Total		400

In 297 out of 4,986 pregnancies with AED monotherapy one or more birth defects were observed (5.9%), as opposed to 100 out of 1,175 pregnancies with AED polytherapy (8.5%) as shown in Table 8.

Table 8 *In this table, denominator excludes both spontaneous abortions and a further 77 untreated cases*

	Monotherapy	%	Polytherapy	%	Total
MCM	261	5.2	93	7.9	354 (5.7%)
CHR	32	0.6	6	0.5	38 (0.6%)
Syndromes	4	0.2	1	0.1	5 (0.1%)
No malformation	4,689	94.0	1,075	91.5	5764 (93.6%)
Total	4,986	100	1,175	100	6161

Outcome in relation to exposure to individual drugs or specific drug combinations is presently being analyzed. This work has, however, not been completed in time to be included in the present interim report.

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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