EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report – May 2018

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BACKGROUND

A number of independent groups with experience and interest in maternal and foetal well-being in association with maternal use of antiepileptic drugs (AEDs) 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, Latin America and Africa.

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 an 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.

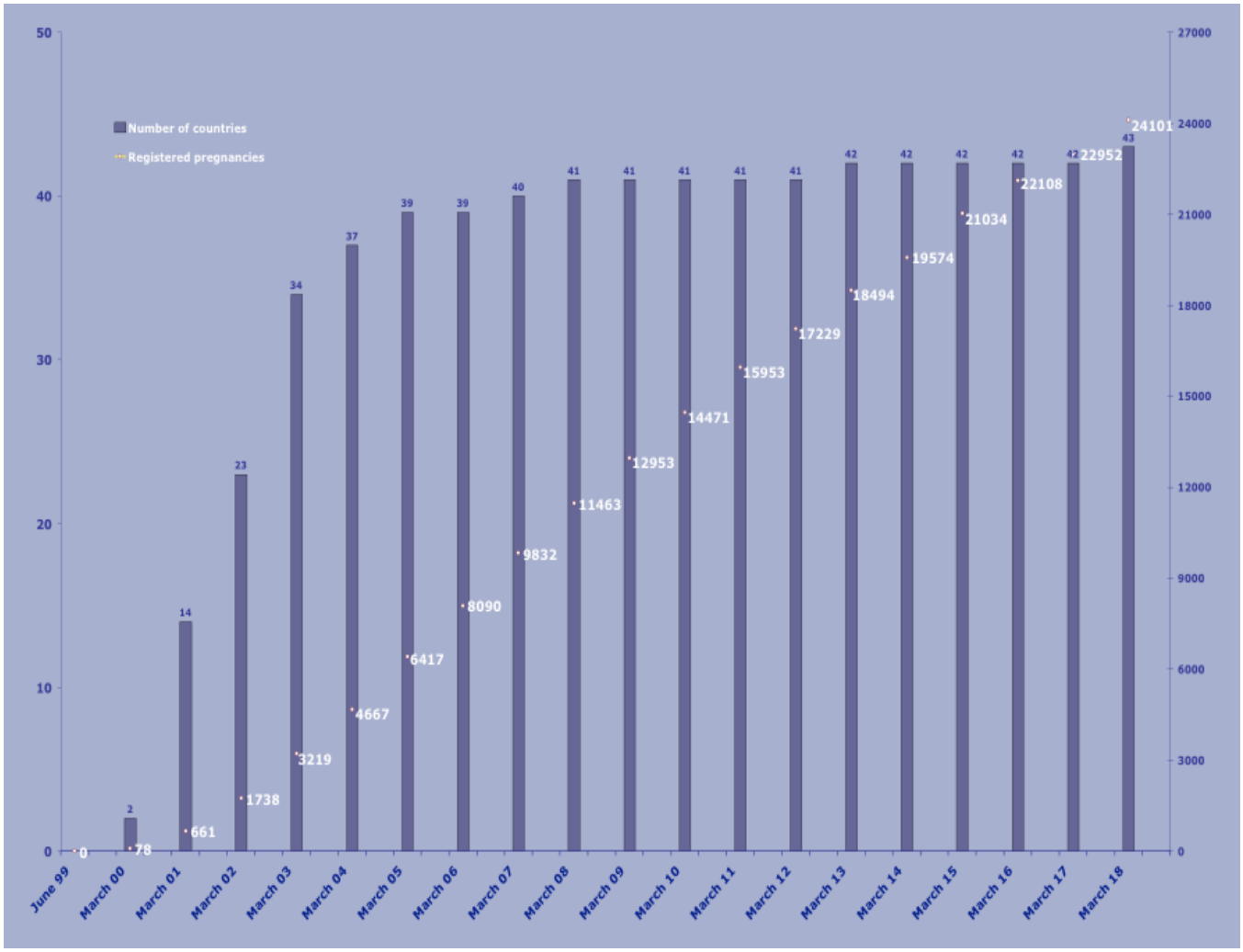
EVALUATION OF OUTCOME

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.

INTERIM REPORT

EURAP was implemented in the first two countries in Europe in 1999 and has since then grown to include countries from Europe, Oceania, Asia, Latin America and Africa. 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 by March, 2018.



The present report is **based on data available in the Central Registry by May 22nd, 2018**.
At that time more than 1,500 reporting physicians from 43 countries had contributed cases to the Central Registry. Countries that have contributed at least 10 pregnancies in the current report are listed in Table 1.

Table 1. Countries that have contributed at least 10 pregnancies in the current report (n=34).

COUNTRY	National Coordinator (or referring physician*)	Date of joining the Registry
Argentina	Silvia Kochen	2002
Australia	Frank Vajda	2000
Austria	Gerhard Luef	2000
Belgium	Dick Lindhout & Eugène van Puijenbroek	2002
Chile	Alejandro De Marinis	2002
China	Weiping Liao	2006
Croatia	Dinko Vitezic	2002
Czech Republic	Jana Zarubova	2001
Denmark	Anne Sabers	2000
Finland	Reetta Kälviäinen	2003
France	Aileen McGonigal*	2000
Georgia	Ketevan Khomeriki	2000
Germany	Bettina Schmitz	2000
Hong-kong	Patrick Kwan	2002
India	Sanjeev Thomas	2001
Israel	Miri Neufeld	2000
Italy	Luigi M. Specchio	2000
Japan	Hideyuki Ohtani	2001
Lithuania	Ruta Mameniskiene	2002
Macedonia	Gordana Kiteva Trencevska	2001
Netherlands	Dick Lindhout & Eugène van Puijenbroek	2002
Norway	Silje Alvestad	2000
Philippines	Leonor Cabral-Lim	2003
Poland	Joanna Jedrzejczak	2001
Portugal	Isabel Pires*; Joana Parra*; Ines Cunha*; Elia Baeta*; Carla Bentes*; Catarina Cruto*	2001
Serbia & Montenegro	Maja Milovanovic	2002
Slovakia	Vladimír Safcák	2002
Slovenia	Boštjan Čebular & Gal Granda	2002
Spain	Meritxell Martinez Ferri	2001
Sweden	Torbjörn Tomson	2000
Switzerland	Barbara Tettenborn & Martin Kurthen; Dominique Flügel*	2001
Taiwan	Hsiang-Yu Yu	2004
Turkey	Demet Ilhan Algın	2000
United Kingdom	John Craig & Aline Russell	2001

** referring physicians*

By the cut-off date for this report (May 22nd, 2018), **24,213 pregnancies had been entered into the central database**. Of these, **10,785 pregnancies are excluded** from the present interim report for reasons explained here below:

1. Pregnancies that failed to meet inclusion criteria (n= 155).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n= 3,035).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n= 1,408).
4. Ongoing pregnancies, updated and corrected (n= 584).
5. Retrospective, but completed and corrected (n=4,098). Among these, there are true retrospective pregnancies (n=3,825) and a further two hundred and sixty pregnancies (n=273) that otherwise met our criteria for prospective pregnancies since they were recruited within 16th week, but for which patients had an ultrasound examination performed before enrolment.
6. Retrospective, i.e. initially classified as prospective pregnancies but re-classified as retrospective cases because one or more CRF subforms were submitted after the set deadlines (n=364).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=56). This includes 1 stillbirth with unknown fetal status, induced abortions with insufficient information on fetus (n=6), anomalies in livebirths where the information was insufficient to determine if qualifying for malformation diagnosis (n=45), 1 incomplete spontaneous abortion with unclear results of biopsy, and 3 perinatal deaths in premature births (<35 gestational weeks) with anomalies difficult to classify as congenital or due to prematurity.
8. Not yet classified, i.e. pregnancies which classification is pending as well as pregnancies which became completed after the last time we sent the database to the Outcome Assessment Committee (OAC), regardless if they contained some malformations or not (n=92).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=993).

Thus in total **13,428 prospective pregnancies** (enrolled at the latest during the 16th gestational week and before outcome is known) **are included** in this report.

The classification of the epilepsy among the prospective pregnancies is given in table 2. Epilepsy was the indication for treatment in all but 108 (1%) of the pregnant women.

Table 2. **Classification of the Epilepsy in 13,428 Prospective Pregnancies.**

Epilepsy	**N**	**%**
Localisation-related*	7,109	52.9
Generalized	5,531	41.2
Undetermined	437	3.3
Missing information	243	1.8
No epilepsy	108	0.8
Total	**13,428**	**100**

**Focal, according to more current terminology.*

The **maternal age** among prospective cases was **30.0 ±5.1 years** (mean±SD), ranging from 14 to 48 years.

The women were of Caucasian **ethnicity** in 88% and of Asian in 8%.

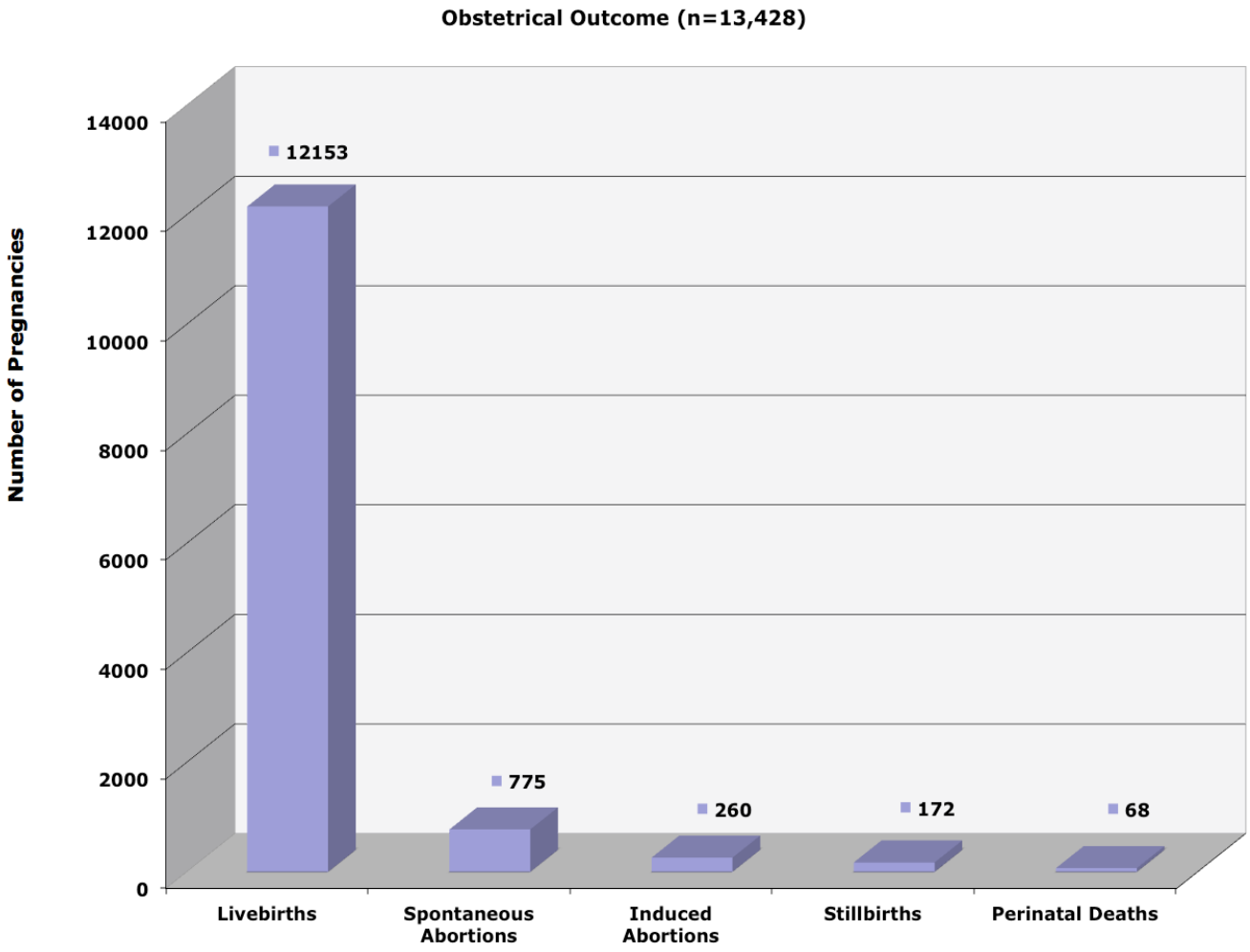
Gravida for each pregnancy is presented in Table 3.

Table 3. **Number of the Pregnancy in Prospective Cases.**

Gravida	**N**	**%**
1st pregnancy	6,114	45.5
2nd pregnancy	4,198	31.3
3rd pregnancy	1,830	13.6
4th pregnancy	792	5.9
5th pregnancy	299	2.2
> 5th pregnancy	193	1.5
Not ascertained	2	0.0
Total	**13,428**	**100**

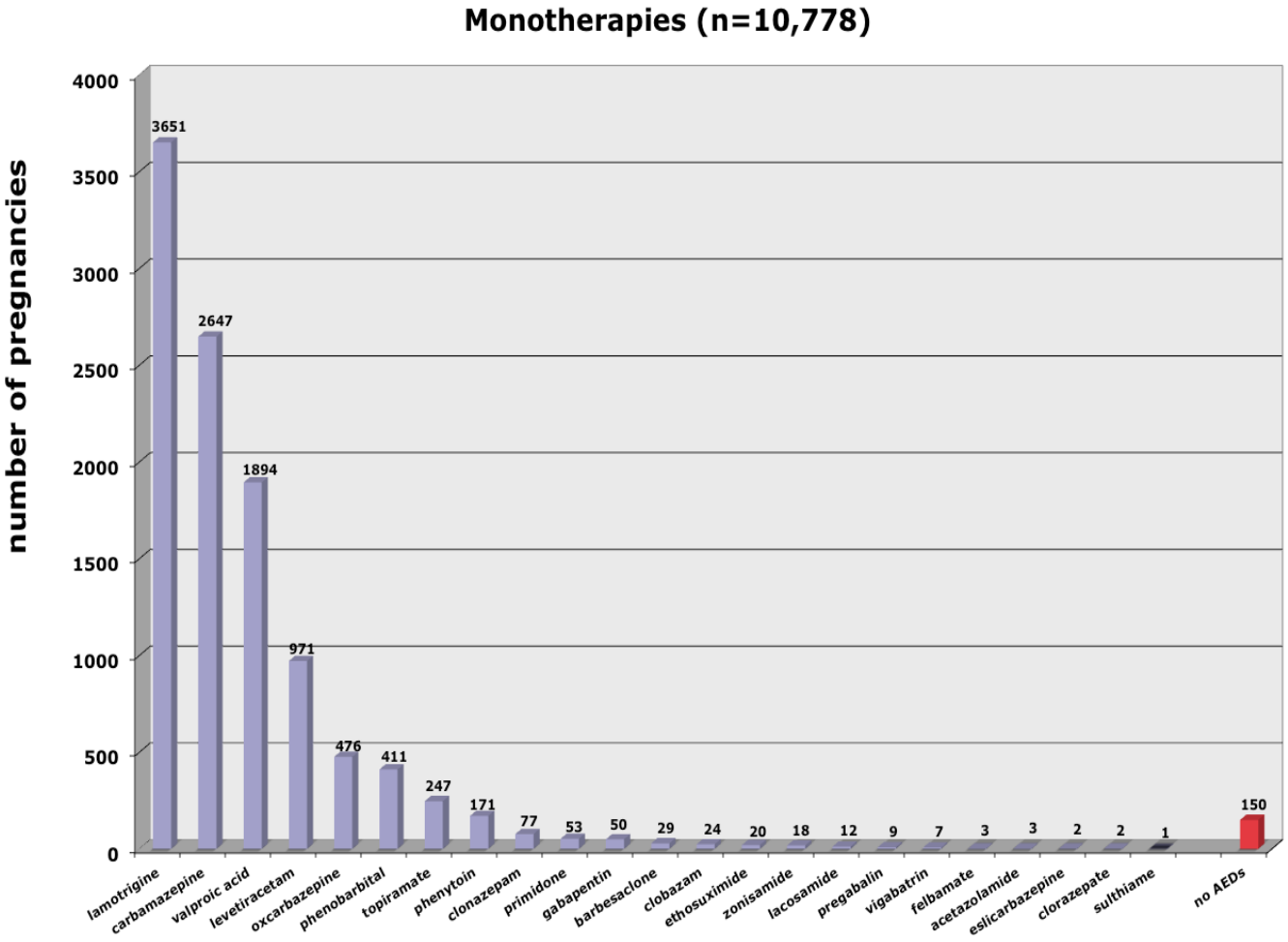
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the **260 induced abortions**, 42 were for chromosomal abnormalities and/or syndromes and 71 were for other fetal indication detected by prenatal screening (*out of these 71 cases, 59 were confirmed as major malformations and the remaining 12 cases were definitively classified as other abnormalities such as hydrops fetalis, molar pregnancies, blighted ovum, fetal placental transfusion syndromes, fetal growth retardation, fetus papyraceus, fetal death for unspecified causes, balanced translocation and insertion in normal individual*).

Figure 2. Obstetrical Outcome of Prospective Pregnancies.



Of the pregnancies, **10,778 (80.3%) involved women on a single AED**, 2,130 (15.9%) were on two AEDs whereas 370 (2.7%) took three AEDs or more. One hundred and fifty women (1.1%) 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 300 different AED combinations. The most frequently used combinations were lamotrigine and valproic acid (n=261), lamotrigine and levetiracetam (n=254), carbamazepine and levetiracetam (n=141), carbamazepine and lamotrigine (n=120), lamotrigine and topiramate (n=89), carbamazepine and valproic acid (n=81), carbamazepine and clobazam (n=78), carbamazepine and phenobarbital (n=76), clobazam and lamotrigine (n=57), levetiracetam and oxcarbazepine (n=53), clonazepam and lamotrigine (n=50) , carbamazepine and topiramate (n=49), and levetiracetam and valproic acid (n=47) (Table 4).

Table 4. The Most Common AED Combinations.

The most common polytherapies	N
lamotrigine + valproic acid	261
lamotrigine + levetiracetam	254
carbamazepine + levetiracetam	141
carbamazepine + lamotrigine	120
lamotrigine + topiramate	89
carbamazepine + valproic acid	81
carbamazepine + clobazam	78
carbamazepine + phenobarbital	76
clobazam + lamotrigine	57
levetiracetam + oxcarbazepine	53
clonazepam + lamotrigine	50
carbamazepine + topiramate	49
levetiracetam + valproic acid	47
lamotrigine + oxcarbazepine	40
topiramate + valproic acid	38
phenobarbital + valproic acid	36
clonazepam + valproic acid	34
carbamazepine + clonazepam	29
phenobarbital + phenytoin	29
levetiracetam + topiramate	27
lamotrigine + phenobarbital	25

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.**

Lamotrigine	1,159
Levetiracetam	746
Topiramate	350
Oxcarbazepine	229
Zonisamide	66
Gabapentin	63
Vigabatrin	37
Pregabalin	26
Tiagabine	10

TERATOGENIC OUTCOME

There were 623 major congenital malformations (MCM), 20 syndromic and/or monogenic cases and 78 chromosomal abnormalities (CHR) in the prospective cohort of 12,653 pregnancies as shown in Table 6 (*775 spontaneous abortions are excluded*).

Table 6. Pathological Outcomes.

Outcome	Outcome Classification	N
MCM	Multiple major	52
	Isolated major	571
MCM		**623**
SYNDROMES or MONOGENIC CONDITIONS		**20**
CHR		**78**
Total		**721**

The 20 syndromic cases are Marfan's syndrome (2), Noonan syndrome (2), inherited tuberous sclerosis (4), Goldenhar syndrome (1), incontinentia pigmenti (2), inherited congenital glaucoma (1), inherited congenital cataract (1), inherited craniosynostosis (1), Di George's syndrome (1), bilateral hearing loss (1), X-linked lissencephaly (1), Skeletal dysplasia/Dwarfism (1), X-linked ichthyosis (1) and Freeman Sheldon syndrome (1).

In this report we will confine our analysis to the 623 MCM including 59 induced abortions, six stillbirths and 16 neonatal deaths. Of the 542 live births, 64 cases of malformations were ascertained prenatally, 330 were first reported at birth, and a further 148 cases not detected at birth but within one year after birth.

Among the 623 cases with MCM, 132 were detected by ultrasound examination. Out of these 132, there were 59 induced abortions, five stillbirths, four perinatal deaths and 64 live births.

The 623 cases represent a **malformation rate of 4.9%** of all prospective pregnancies for which follow-up has been completed (623/12,653).

The type of malformations is described in Table 7.

Table 7

PATHOLOGICAL OUTCOMES	DESCRIPTION	N
MCM	Multiple major	52
	Nervous system	
MCM	Spina Bifida	42
MCM	Anencephalus and similar	4
MCM	Hydrocephaly	5
MCM	Microcephaly	1
MCM	Nervous system (other malformations)	12
MCM	all	64
	Heart	
	Atrial septal defect	36
MCM	Ventricular septal defect	50
MCM	Atrioventricular septal defect	2
MCM	Congenital heart disease	48
MCM	Tetralogy of Fallot	4
MCM	Transposition of great vessels (complete)	4
MCM	Pulmonary valve stenosis	9
MCM	Hypoplastic left heart	8
	all	161
	Urinary system	
MCM	Urinary system (other malformations)	43
MCM	Renal Dysplasia	4
	all	47
	Digestive system	
MCM	Diaphragmatic hernia	8
MCM	Ano-rectal atresia and stenosis	2
MCM	Digestive system (other malformations)	9
MCM	Duodenal atresia or stenosis	2
MCM	Gastroschisis	2
MCM	Omphalocele	3
MCM	Atresia of oesophagus without fistula	1
	all	27
	Limbs	
MCM	Upper limb reduction	8
MCM	Lower limb reduction	1
MCM	Syndactyly	5
MCM	Polydactyly	23
MCM	Club foot - talipes equinovarus	18
	all	55
	Musculoskeletal	
MCM	Musculo-skeletal (other malformations)	11
MCM	Hip dislocation and/or dysplasia	68
	all	79
	Genital system	
MCM	Genital (developmental ovarian cyst)	5
MCM	Hypospadias	71
	all	76
	Eye, ear, face and neck	
MCM	Congenital cataract	4
MCM	Eye (other malformations)	3
MCM	Ear, face and neck	5
MCM	Choanal atresia	1
MCM	all	13
	Oro facial clefts	
MCM	Cleft lip with or without palate	13
MCM	Cleft palate	16
	all	29
MCM	**Other specified malformations** (including sacral teratoma, cystic hygroma, haemangiomas, accessory skin tags, aberrant subclavian artery, congenital malformation of spleen, sequences, genetic syndromes)	20
MCM	**all MCMs**	**623**
	Chromosomal	
CHR	Chromosomal	20
CHR	Down's syndrome	39
CHR	Edward syndrome/trisomy 18	8
CHR	Klinefelter's syndrome	1
CHR	Patau syndrome/trisomy 13	5
CHR	Turner's syndrome	4
CHR	Wolff-Hirschorn syndrome	1
CHR	**all CHR**	**78**
	Syndromes or monogenic conditions	
Syndrome	Marfan's syndrome	2
Syndrome	Incontinentia pigmenti	2
Syndrome	Noonan's syndrome	2
Syndrome	Goldenhar syndrome (Oculo-auriculo-vertebral syndrome)	1
Syndrome	Di George's syndrome	1
Syndrome	Tuberous sclerosis	4
Syndrome	Craniosynostosis, inherited	1
Syndrome	Congenital cataract, inherited	1
Syndrome	Congenital glaucoma, inherited	1
Syndrome	X-linked Ichthyosis	1
Syndrome	X-linked Lissencephaly	1
Syndrome	Hearing loss, bilateral, inherited	1
Syndrome	Skeletal dysplasia (achondroplastic Dwarfism)	1
Syndrome	Freeman Sheldon Syndrome (distal arthrogryposis type 2A)	1
Syndromes	**all Syndromes**	**20**
Total	**all cases with pathological outcomes**	**721**

In 463 out of 10,192 pregnancies with AED monotherapy, one or more MCMs were observed (4.5%) as opposed to 156 out of 2,316 pregnancies with AED polytherapy (6.7 %), as shown in Table 8.

Table 8. Pathological Outcomes by AED Treatment Categories.
(In this table, 775 spontaneous abortions have been excluded from the denominator).

	No AED	%	Monotherapy	%	Polytherapy	%	Total
MCM	**4**	2.8	**463**	4.5	**156**	6.7	**623 (**4.9%**)**
CHR	**1**	0.7	**64**	0.6	**13**	0.6	**78 (**0.6%**)**
Syndromes	**0**	0.0	**16**	0.2	**4**	0.2	**20 (**0.2%**)**
No malformation	**140**	96.5	**9,649**	94.7	**2,143**	92.5	**11,932 (**94.3%**)**
Total	**145**	100	**10,192**	100	**2,316**	100	**12,653 (**100%**)**

PUBLICATIONS

Outcome regarding the eight most common monotherapies has been published in Lancet Neurology, April 18, 2018.

The dose-dependent risk of MCM with exposure to valproate in mono- and polytherapy has also been analysed and reported (*Neurology, Sept 8, 2015*) and so has the risk of intrauterine death in association with different treatments (*Neurology Aug 18, 2015*).

A manuscript on seizure control in pregnancies with withdrawal of or switch from valproate during 1st trimester as compared with maintained valproate treatment has been published in Epilepsia (*Epilepsia 2016; 57: e173-7*).

Outcome in relation to exposure to individual drugs or specific drug combinations is not included in the present 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, Bial, Sanofi-Synthelabo, Novartis and UCB Pharma. In addition, national and regional networks may receive support from the same or other pharmaceutical companies.

APPENDIX

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