# EURAP

## An International Antiepileptic Drugs and Pregnancy Registry

Interim Report - November 2016

**Central Study Coordinator**
Dr. Dina Battino
*Department of Neurophysiology and Experimental Epileptology*
*I.R.C.C.S. Neurological Institute ''Carlo Besta'' Foundation*
*20 133 Milano,* ***Italy***
Tel: + 39-02-23-94-22-30
Fax: + 39-02-700-42-91-60
E-mail: eurap@istituto-besta.it

**Chairman Central Project Commission**
Dr. Torbjörn Tomson
*Department of Neurology*
*Karolinska University Hospital*
*S-171 76 Stockholm,* ***Sweden***
Tel: + 46-08-51-77-37-05
Fax: + 46-08-51-77-37-57
E-mail: torbjorn.tomson@karolinska.se

## 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.

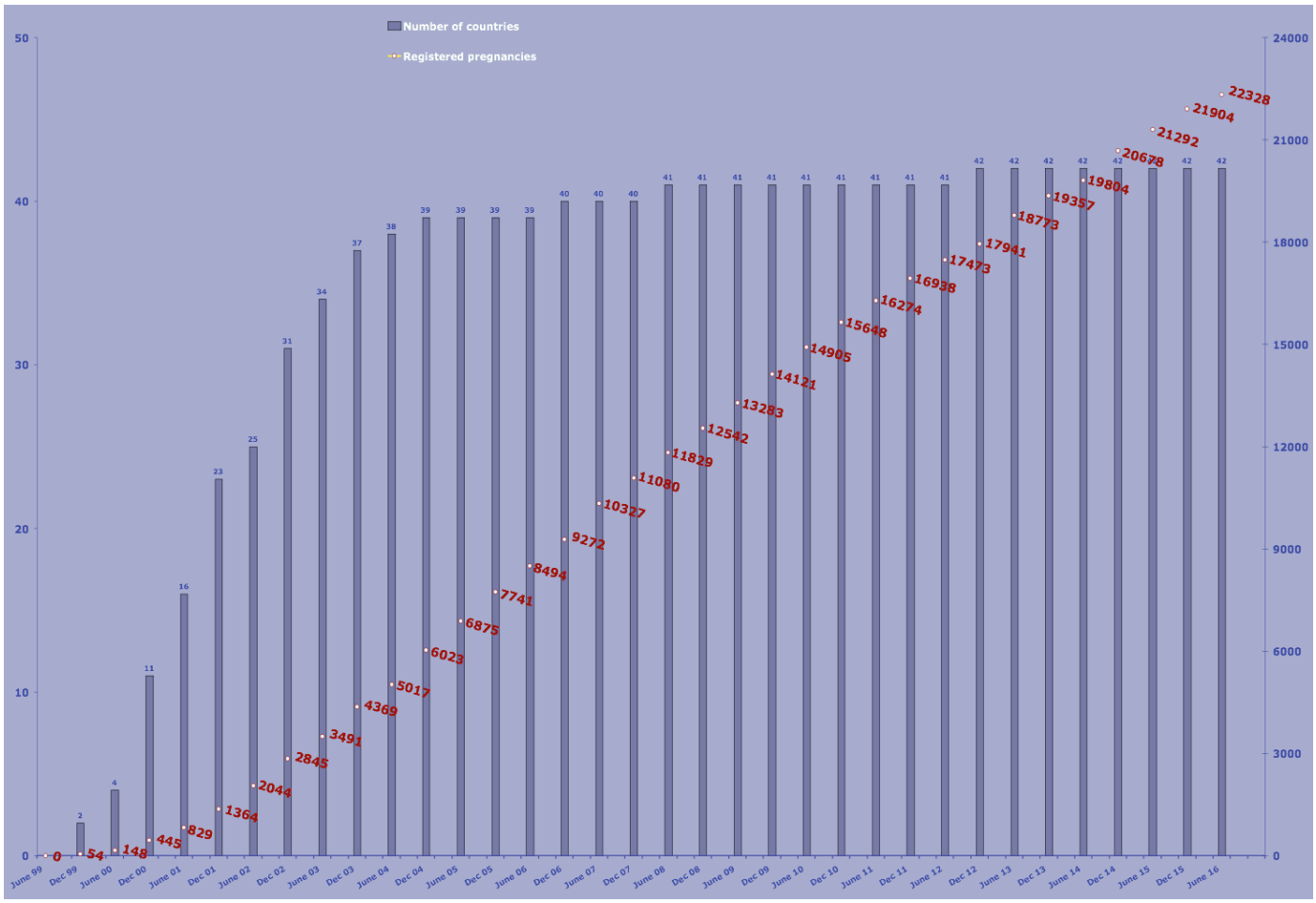
## EVALUATION OF OUTCOME

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 June, 2016.**




The present report is **based on data available in the Central Registry by November 16th, 2016**. At that time more than 900 reporting physicians from 42 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; Irena Novotna | 2001 |
| Denmark | Anne Sabers | 2000 |
| Finland | Reetta Kälviäinen | 2003 |
| France | Aileen McGonigal* | 2000 |
| Georgia | Sofia Kasradze; Otar Toidze | 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 | Karl-Otto Nakken | 2000 |
| Philippines | Leonor Cabral-Lim | 2003 |
| Poland | Joanna Jedrzejczak | 2001 |
| Portugal | Isabel Pires*; Luis Isidoro*; Elia Baeta* | 2001 |
| Serbia & Montenegro | Maja Milovanovic | 2002 |
| Slovakia | Vladimír Safcák | 2002 |
| Slovenia | Boštjan Čebular | 2002 |
| Spain | Meritxell Martinez Ferri | 2001 |
| Sweden | Torbjörn Tomson | 2000 |
| Switzerland | Barbara Tettenborn & Martin Kurthen; Dominique Flügel* | 2001 |
| Taiwan | Chi Wan Lai & Alice Yu | 2004 |
| Turkey | Çigdem Özkara; Demet Ilhan Algın | 2000 |
| United Kingdom | John Craig & Aline Russell | 2001 |

* referring physicians

By the cut-off date for this report (November 16th, 2016), **22,639 pregnancies had been entered into the central database**. Of these, **10,098 pregnancies are excluded** from the present interim report for reasons explained here below:

1. Pregnancies that failed to meet inclusion criteria (n= 144).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n= 2,954).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n= 1,041).
4. Ongoing pregnancies, updated and corrected (n= 598).
5. Retrospective, but completed and corrected (n=3,958). Among these, there are true retrospective pregnancies (n=3,698) and a further two hundred and sixty pregnancies (n=260) that otherwise met our criteria for prospective pregnancies since they were recruited within 16$^{th}$ week, but 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=353).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=51). 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=40), 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=52).
9. Treatment changes between different AEDs or mono- to polytherapy or vice versa during the first trimester (n=947).

Thus in total **12,541 prospective pregnancies** (enrolled at the latest during the 16$^{th}$ 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 107 (1%) of the pregnant women.

**Table 2**. **Classification of the Epilepsy in 12,541 Prospective Pregnancies.**

| **Epilepsy** | **N** | **%** |
|---|---|---|
| Localisation-related* | 6,648 | 53.0 |
| Generalized | 5,157 | 41.1 |
| Undetermined | 401 | 3.2 |
| Missing information | 228 | 1.8 |
| No epilepsy | 107 | 0.9 |
| **Total** | **12,541** | **100** |

The **maternal age** among prospective cases was **29.9 ±5.1 years** (mean±SD), ranging from 14 to 46 years.

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

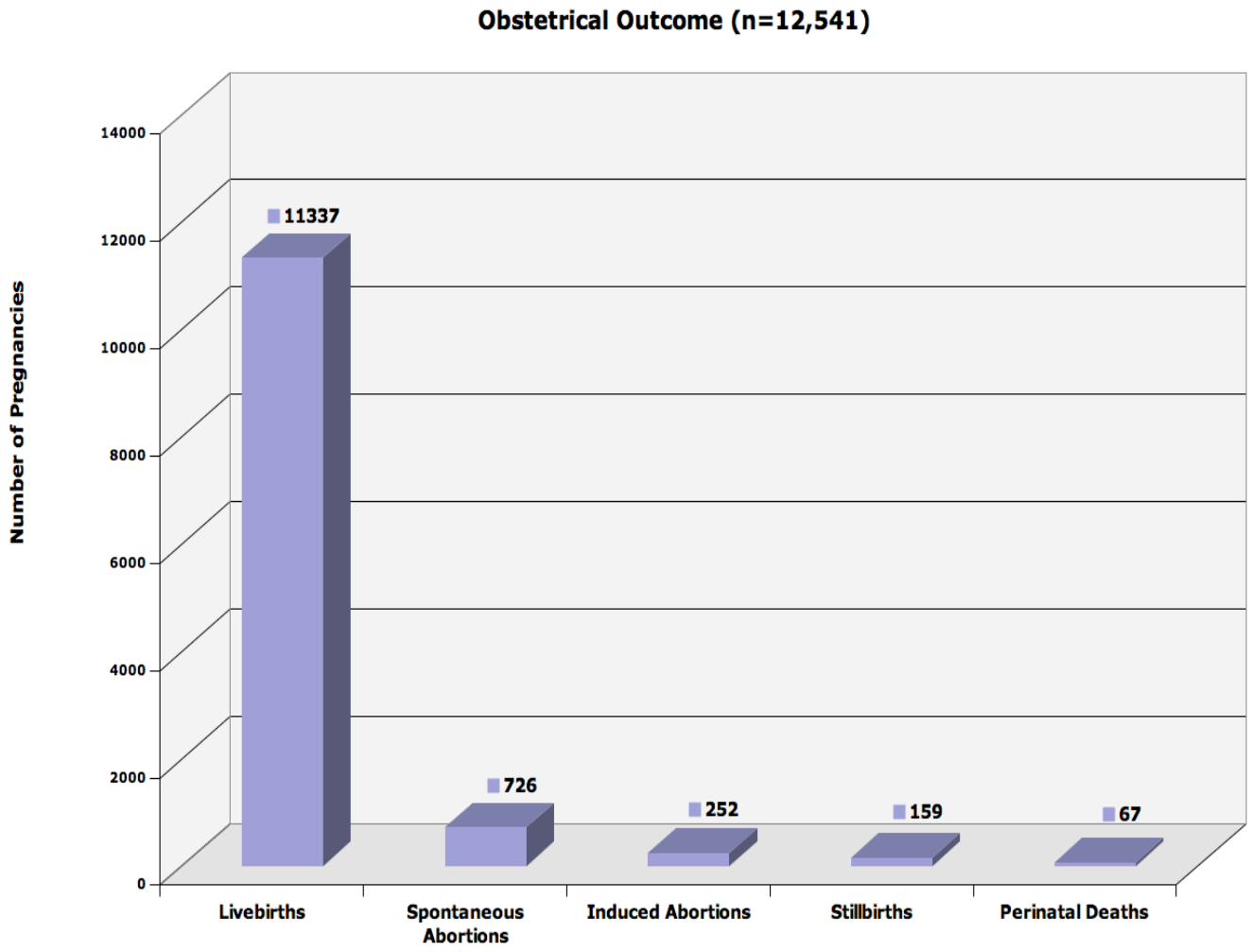
**Gravida for each pregnancy** is presented in Table 3.

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

| **Gravida** | **N** | **%** |
|---|---|---|
| 1st pregnancy | 5,729 | 45.7 |
| 2nd pregnancy | 3,902 | 31.1 |
| 3rd pregnancy | 1,712 | 13.6 |
| 4th pregnancy | 743 | 6.0 |
| 5th pregnancy | 277 | 2.2 |
| > 5th pregnancy | 177 | 1.4 |
| Not ascertained | 1 | 0.0 |
| **Total** | **12,541** | **100** |

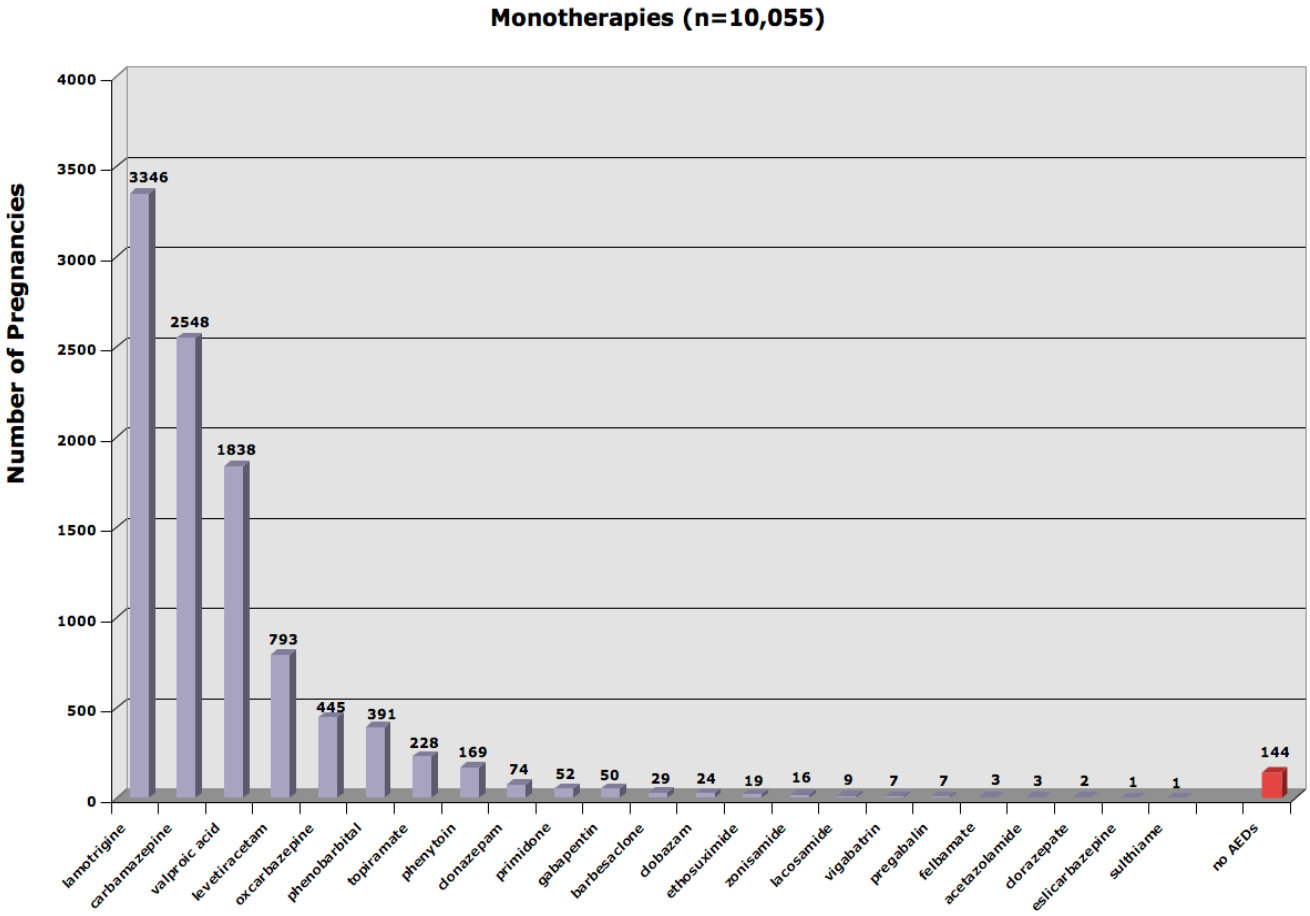
The outcome of the prospective completed pregnancies is presented in Figure 2. Out of the **252 induced abortions**, 38 were for chromosomal abnormalities and/or syndromes and 69 were for other fetal indication detected by prenatal screening (*out of these 69 cases, 57 were confirmed as major malformations 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,…etc*).

**Figure 2. Obstetrical Outcome of Prospective Pregnancies.**




Of the pregnancies, **10,055 (80.2%) involved women on a single AED**, 1,997 (15.9%) were on two AEDs whereas 345 (2.8%) took three AEDs or more. One hundred and forty-four 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 282 different AED combinations**. The most frequently used combinations were lamotrigine and valproic acid (n=253), lamotrigine and levetiracetam (n=215), carbamazepine and levetiracetam (n=136), carbamazepine and lamotrigine (n=118), lamotrigine and topiramate (n=82), carbamazepine and valproic acid (n=81), carbamazepine and phenobarbital (n=75), carbamazepine and clobazam (n=74), clobazam and lamotrigine (n=54), carbamazepine and topiramate (n=47), levetiracetam and oxcarbazepine (n=47), clonazepam and lamotrigine (n=47) and levetiracetam and valproic acid (n=46) (Table 4).

**Table 4. The Most Common AED Combinations.**

| The most common polytherapies | N |
|---|---|
| lamotrigine + valproic acid | 253 |
| lamotrigine + levetiracetam | 215 |
| carbamazepine + levetiracetam | 136 |
| carbamazepine + lamotrigine | 118 |
| lamotrigine + topiramate | 82 |
| carbamazepine + valproic acid | 81 |
| carbamazepine + phenobarbital | 75 |
| carbamazepine + clobazam | 74 |
| clobazam + lamotrigine | 54 |
| carbamazepine + topiramate | 47 |
| clonazepam + lamotrigine | 47 |
| levetiracetam + oxcarbazepine | 47 |
| levetiracetam + valproic acid | 46 |
| topiramate + valproic acid | 38 |
| lamotrigine + oxcarbazepine | 38 |
| phenobarbital + valproic acid | 36 |
| clonazepam + valproic acid | 33 |
| phenobarbital + phenytoin | 28 |
| carbamazepine + clonazepam | 28 |
| lamotrigine + phenobarbital | 23 |
| levetiracetam + topiramate | 22 |

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 | 1,077 |
| Levetiracetam | 655 |
| Topiramate | 327 |
| Oxcarbazepine | 213 |
| Gabapentin | 62 |
| Zonisamide | 52 |
| Vigabatrin | 37 |
| Pregabalin | 22 |
| Tiagabine | 9 |

## TERATOGENIC OUTCOME

There were 595 major congenital malformations (MCM), 20 syndromic and/or monogenic cases and 71 chromosomal abnormalities (CHR) in the prospective cohort of 11,815 pregnancies as shown in Table 6 (*726 spontaneous abortions are excluded*).

**Table 6. Pathological Outcomes.**

| Outcome | Outcome Classification | N |
|---|---|---|
| **MCM** | Multiple major | 52 |
| | Isolated major | 543 |
| **MCM** | | **595** |
| | | |
| **SYNDROMES or MONOGENIC CONDITIONS** | | **20** |
| | | |
| **CHR** | | **71** |
| | | |
| **Total** | | **686** |

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 595 MCM including 57 induced abortions, six stillbirths and 16 neonatal deaths. Of the 516 live births, 54 cases of malformations were ascertained prenatally, 319 were first reported at birth, and a further 143 cases not detected at birth but within one year after birth.

Among the 595 cases with MCM, 114 were detected by ultrasound examination. Out of these 114, there were 52 induced abortions, four stillbirths, four perinatal deaths and 54 live births.

The 595 cases represent a **malformation rate of 5.0%** of all prospective pregnancies for which follow-up has been completed (595/11,815).

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 | 3 |
| MCM | Hydrocephaly | 5 |
| MCM | Microcephaly | 1 |
| MCM | Nervous system (other malformations) | 12 |
| MCM | all | **63** |
| | **Heart** | |
| | Atrial septal defect | 36 |
| MCM | Ventricular septal defect | 48 |
| MCM | Atrioventricular septal defect | 2 |
| MCM | Congenital heart disease | 46 |
| MCM | Tetralogy of Fallot | 4 |
| MCM | Transposition of great vessels (complete) | 4 |
| MCM | Pulmonary valve stenosis | 9 |
| MCM | Hypoplastic left heart | 6 |
| | all | **155** |
| | **Urinary system** | |
| MCM | Urinary system (other malformations) | 39 |
| MCM | Renal Dysplasia | 3 |
| | all | **42** |
| | **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 |
| | Omphalocele | 3 |
| | all | **26** |
| | **Limbs** | |
| MCM | Upper limb reduction | 7 |
| MCM | Syndactyly | 5 |
| MCM | Polydactyly | 22 |
| MCM | Club foot - talipes equinovarus | 18 |
| | all | **52** |
| | **Musculoskeletal** | |
| MCM | Musculo-skeletal (other malformations) | 8 |
| MCM | Hip dislocation and/or dysplasia | 65 |
| | all | **73** |
| | **Genital system** | |
| MCM | Genital (developmental ovarian cyst) | 5 |
| MCM | Hypospadias | 67 |
| | all | **72** |
| | **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) | **18** |
| **MCM** | **all MCMs** | **595** |
| | **Chromosomal** | |
| CHR | Chromosomal | 17 |
| CHR | Down's syndrome | 35 |
| 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** | **71** |
| | **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 or Monogenic Conditions** | **all Syndromes** | **20** |
| **Total** | **Total** | **686** |

In 441 out of 9,506 pregnancies with AED monotherapy, one or more MCMs were observed (4.6%) as opposed to 151 out of 2,170 pregnancies with AED polytherapy (7.0 %), as shown in Table 8.

**Table 8. Pathological Outcomes by AED Treatment Categories.**
*(In this table, 726 spontaneous abortions have been excluded from the denominator).*

| | No AED | % | Monotherapy | % | Polytherapy | % | Total |
|---|---|---|---|---|---|---|---|
| **MCM** | **3** | 2.2 | **441** | 4.6 | **151** | 7.0 | **595 (**5.0%**)** |
| **CHR** | **1** | 0.7 | **58** | 0.6 | **12** | 0.5 | **71 (**0.6%**)** |
| **Syndromes** | **0** | 0.0 | **16** | 0.2 | **4** | 0.2 | **20 (**0.2%**)** |
| **No malformation** | **135** | 97.1 | **8,991** | 94.6 | **2,003** | 92.3 | **11,129 (**94.2%**)** |
| **Total** | **139** | 100 | **9,506** | 100 | **2,170** | 100 | **11,815 (**100%**)** |

Outcome regarding the four most common monotherapies has been published in Lancet Neurology, June 6, 2011. 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 recently 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

## Central Project Commission

Dina Battino, Milano

Erminio Bonizzoni, Pavia

John Craig, Belfast

Dick Lindhout, Utrecht

Emilio Perucca, Pavia

Anne Sabers, Copenhagen

Sanjeev V Thomas, Trivandrum

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

(*The persons below have contributed to the work of the OAC during different time periods of the project*)

Elisabeth Robert-Gnansia, Lyon, France

Richard Finnell, Houston, Texas

Francesca Faravelli, Genoa, Italy

Chiara Pantaleoni, Milan, Italy