EURAP

An International Antiepileptic Drugs and Pregnancy Registry

Interim Report Germany – MAY 2024

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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 antiseizure medications (ASMs) have agreed on a prospective international multi-centre study of pregnancies with ASMs. 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. The EURAP Study protocol has been updated in June 2021 and can be found on www.eurapinternational.org

OBJECTIVE OF EURAP

The primary objective of EURAP is to evaluate and determine the comparative risk of major foetal malformations following intake of ASMs and their combinations during pregnancy.

METHODS

EURAP is an observational study. Women taking ASMs 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 Figure 1.

Figure 1. Number of Participating Countries and Pregnancies Reported to the Central Registry by May, 2024.

The present report is **based on data available in the Central Registry by May 27th, 2024**. At that time more than 1,500 reporting physicians from 47 countries had contributed cases to the Central Registry. Table 1 shows the number of cases included in the May 2024 interim report, for each country.

Table 1. Countries with pregnancies included in the current report (n=43)

COUNTRY	INCLUDED CASES
Italy	2,616
Germany	**2,193**
Denmark	1,520
Norway	1,485
Netherlands	1,465
Sweden	1,434
India	812
Australia	808
Spain	741
Czech Republic	717
Japan	553
Finland	475
Austria	442
United Kingdom	366
Serbia & Montenegro	360
Switzerland	219
Taiwan	185
Slovakia	180
Chile	168
Turkey	119
Israel	108
Slovenia	99
Belgium	92
Lithuania	84
Macedonia	79
Georgia	78
Iran	76
Argentina	75
Portugal	64
Philippines	47
France	31
Croatia	27
Poland	26
Estonia	24
China	19
El Salvador	18
Belarus	12
Hong-kong	12
Hungary	6
Albania	1
Algeria	1
Russia	1
Ukraine	1
TOTAL	**17,839**

By the cut-off date for this report (May 27th, 2024), **4,703 pregnancies from Germany had been entered into the central database**. Of these, **2,510 pregnancies are excluded** from the present interim report for reasons explained here below:

1. Pregnancies that failed to meet inclusion criteria (n=63).
2. Lost to follow-up, including those failing to submit sub-forms within preset deadlines (n=1,448).
3. Pending pregnancies, awaiting updates or corrections of different sub-forms (n=243).
4. Ongoing pregnancies, updated and corrected (n=160).
5. Retrospective, but completed and corrected (n=300). Among these, there are true retrospective pregnancies (n=271) and a further twenty-nine pregnancies (n=29) 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=67).
7. Unclassifiable i.e. cases for which it was impossible to determine if there was a malformation or not (n=15). This includes 1 induced abortion with insufficient information on fetus, and anomalies in 14 live births where the information were insufficient to determine if qualifying for malformation diagnosis (*i.e. 1 case with suspected cornelia de lange syndrome,1 case without a clear diagnosis, 2 cases with an unspecified congenital heart defect, 2 cases with an emangioma but missing information on size, 2 cases with dermal sinus, 1 case with ventricular brain asymmetry, 3 cases with atrial septal defect without follow-up after birth and 2 cases with pyelectasia but missing information about size of pelvic dilatation*).
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=23).
9. Treatment changes between different ASMs or mono- to polytherapy or vice versa during the first trimester (n=191).

Thus, in total **2,193 prospective pregnancies** (enrolled at the latest during the 16th gestational week and before outcome was known) **are included** in this report.

The indication for treatment and the classification of the epilepsy among the prospective pregnancies are reported in table 2. Epilepsy was the indication for treatment in all but 11 (0.5%) of the pregnancies.

Table 2. Classification of the epilepsy in 2,193 prospective pregnancies.

Epilepsy	**N**	**%**
Localisation-related*	1,066	48.6
Generalized	970	44.2
Undetermined	79	3.6
Missing information	67	3.1
No epilepsy	11	0.5
Total	**2,193**	**100**

**Focal, according to current ILAE terminology.*

The women were of Caucasian **ethnicity** in 93,4% and of Asian in 1,5%.

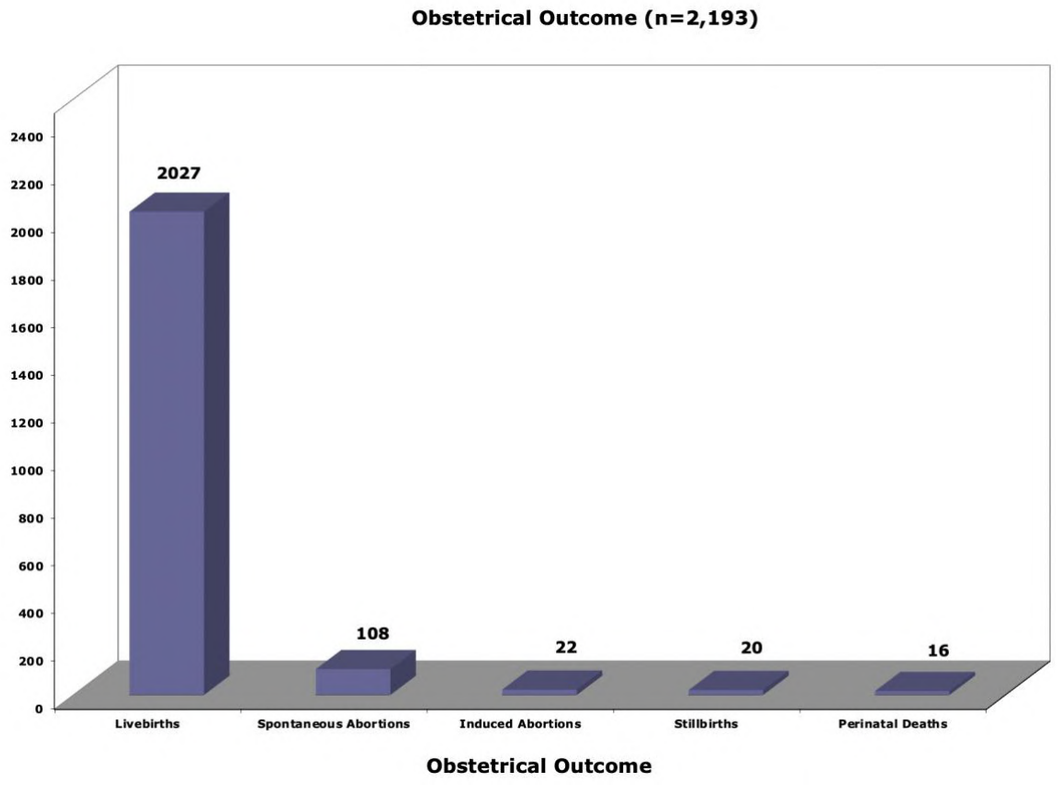
Gravida for each pregnancy is reported in Table 3.

Table 3. Number of the pregnancy in 2,193 prospective cases.

Gravida	N	%
1st pregnancy	1,149	52.4
2nd pregnancy	654	29.8
3rd pregnancy	250	11.4
4th pregnancy	92	4.2
5th pregnancy	32	1.4
> 5th pregnancy	15	0.7
Not ascertained	1	0.1
Total	**2,193**	**100**

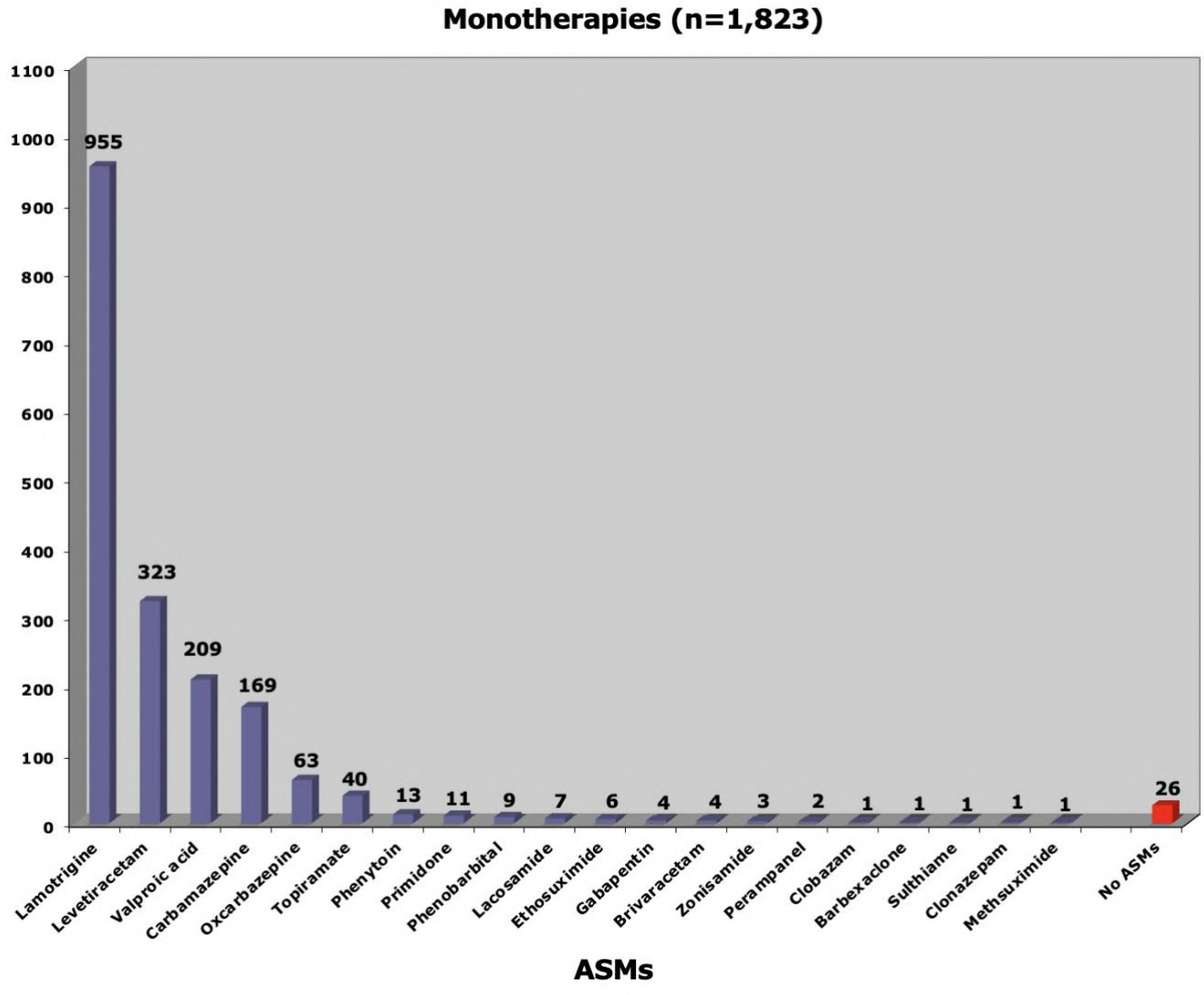
The outcomes of the prospective completed pregnancies are illustrated in Figure 2. Out of the **22 induced abortions cases**, 11 cases were due to maternal reasons (either social or medical), 6 cases were for chromosomal abnormalities and/or syndromes and 5 cases were due to other fetal indications detected by prenatal screening (*out of these 5 cases, 3 were finally confirmed as major malformations and 2 cases were classified as other abnormalities such as fetal growth retardation and unverifiable foetus*).

Figure 2. Obstetrical outcome of prospective pregnancies.



Of the 2,193 pregnancies, **1,823 (83.1%) involved women on a single ASM**, 308 (14.1%) women on two ASMs, whereas 36 (1.6%) took three ASMs or more. Twenty-six women (1.2%) were not on ASM treatment during the 1st trimester. The exposure to the different ASMs in monotherapy among the prospective pregnancies is illustrated in Figure 3.

Figure 3. **Number of prospective pregnancies exposed to different ASMs in monotherapy during the first trimester of pregnancy.**



There were 86 different ASM combinations. The most frequently used combinations were lamotrigine and levetiracetam (n=122), lamotrigine and valproic acid (n=25), levetiracetam and valproic acid (n=18), lacosamide and levetiracetam (n=16), levetiracetam and oxcarbazepine (n=16), carbamazepine and levetiracetam (n=12), lamotrigine and topiramate (n=8), carbamazepine and lamotrigine (n=5), lamotrigine and oxcarbazepine (5), levetiracetam and phenobarbital (n=4), lamotrigine and zonisamide (n=4), topiramate and valproic acid (n=4), carbamazepine and valproic acid (n=4) and levetiracetam and topiramate (n=4) (Table 4).

Table 4. Most common ASM combinations recorded in prospective pregnancies.

Most common polytherapies during the first trimester of pregnancy	N
lamotrigine + levetiracetam	122
lamotrigine + valproic acid	25
levetiracetam + valproic acid	18
lacosamide + levetiracetam	16
levetiracetam + oxcarbazepine	16
carbamazepine + levetiracetam	12
lamotrigine + topiramate	8
carbamazepine + lamotrigine	5
lamotrigine + oxcarbazepine	5
levetiracetam + phenobarbital	4
lamotrigine + zonisamide	4
topiramate + valproic acid	4
carbamazepine + valproic acid	4
levetiracetam + topiramate	4
carbamazepine + phenobarbital	3
lamotrigine + phenytoin	3
lamotrigine + levetiracetam + valproic acid	3
lamotrigine + levetiracetam + oxcarbazepine	3

The number of pregnancies exposed to different second-generation ASMs taken in combination with other ASMs are listed in Table 5.

Table 5. Number of pregnancies exposed to second-generation ASMs in a polytherapy regimen.

Levetiracetam	221
Lamotrigine	206
Oxcarbazepine	36
Topiramate	27
Lacosamide	27
Zonisamide	11
Perampanel	8
Brivaracetam	7
Pregabalin	7
Gabapentin	4
Rufinamide	2
Tiagabine	1
Vigabatrin	1
Eslicarbazepine acetate	1
Retigabine	0

TERATOGENIC OUTCOME

There were 97 cases of major congenital malformations (MCMs), 5 syndromic and/or genetic cases and 9 chromosomal abnormalities (CHR) in the prospective cohort of 2,085 pregnancies for which follow-up has been completed, as shown in Table 6 (*108 spontaneous abortions are excluded*).

Table 6. Pathological outcomes.

Outcome	Outcome Classification	N
MCMs	Multiple major	7
	Isolated major	90
MCMs		**97**
Syndromes or genetic conditions		**5**
CHR		**9**
Total		**111**

The 5 syndromic and/or genetic cases include inherited tuberous sclerosis (1), incontinentia pigmenti (Bloch-Sulzberger syndrome) (1), inherited congenital cataract (1), Zellweger syndrome (1) and achondroplasia (1).

In this report we confine our analysis to the 97 MCMs including those identified in 3 induced abortions, 3 neonatal deaths and 91 live births. Of the 91 live births, 12 cases of malformations were ascertained prenatally, 57 were first reported at birth, and a further 22 cases not detected at birth were identified within one year after birth.

Among the 97 cases with MCMs, 17 were detected by ultrasound examination. Out of these 17 cases, there were 3 induced abortions, 2 neonatal deaths and 12 live births.

The 97 cases represent an **MCM prevalence of 4.7%** of all prospective pregnancies for which follow-up has been completed (97/2,085).

The type of MCMs, CHR, genetic conditions, and other syndromes are described in Table 7.

Table 7

PATHOLOGICAL OUTCOMES	DESCRIPTION	N
MCM	Multiple major	7
	Cardiovascular system	
MCM	Atrial septal defect	2
MCM	Patent ductus arteriosus	3
MCM	Congenital pulmonary valve stenosis	2
MCM	Pulmonary valve atresia	1
MCM	Hypoplastic left heart syndrome	1
MCM	Ventricular septal defect	12
MCM	Congenital malformations of the heart, unspecified	1
MCM	Other congenital malformations of aorta; Atrial septal defect	1
	all	**23**
	Genital system	
MCM	Developmental ovarian cyst, single	1
MCM	Developmental ovarian cyst, multiple	1
MCM	Hypospadias	9
MCM	Other specified congenital malformations of female genitalia	1
	all	**12**
	Nervous system	
MCM	Spina Bifida	3
MCM	Single congenital cerebral cyst	1
MCM	Congenital celebral cysts	4
	all	**8**
	Musculoskeletal	
MCM	Hip dislocation and/or dysplasia	15
	all	**15**
	Urinary system	
MCM	Atresia and stenosis of ureter	1
MCM	Accessory kidney	1
MCM	Congenital deformity of urinary system, NOS	1
MCM	Congenital megaloureter	2
MCM	Congenital pelviureteric junction obstruction, unilateral	1
MCM	Patent urachus	1
MCM	Impervious urethra (Megacystis-megaureter syndrome)	1
MCM	Double or triple kidney	1
MCM	Congenital hydronephrosis; Congenital posterior urethral valves	1
MCM	Other cystic kidney disease	1
MCM	Potter's syndrome	1
	all	**12**
	Digestive system	
MCM	Imperforate anus	1
MCM	Congenital cardiospam	1
MCM	Congenital absence, atresia and stenosis of duodenum	1
MCM	Duplication of anus, appendix, caecum and intestine	1
MCM	Atresia of oesophagus without fistula	2
MCM	Hirschsprung's disease	2
	all	**8**
	Eye, Ear, Face and Neck	
MCM	Congenital absence, atresia and stricture of auditory canal (external)	1
MCM	Congenital cataract	1
	all	**2**
	Oro facial clefts	
MCM	Cleft palate	2
	all	**2**
	Limbs	
MCM	Polydactyly	3
	all	**3**
MCM	**Other specified malformations** (*including sacral teratoma, aberrant subclavian artery, congenital malformations of spleen, congenital malfomations of lung, congenital malformations of thyroid gland*)	**5**
MCM	**all MCMs**	**97**
	Chromosomal	
CHR	Chromosomal abnormality (defective chromosomes 4 and 16)	1
CHR	Down's syndrome	2
CHR	Edward syndrome	1
CHR	Klinefelter's syndrome	1
CHR	Patau's syndrome	2
CHR	Turner's syndrome	2
CHR	**all CHR**	**9**
	Syndromes or genetic conditions	
Syndrome	achondroplasia	1
Syndrome	congenital cataract, inherited	1
Syndrome	tuberous sclerosis, inherited	1
Syndrome	incontinentia pigmenti (Bloch-Sulzberger syndrome)	1
Syndrome	Zellweger syndrome	1
Syndromes	**all syndromes or genetic conditions**	**5**
Total		**111**

One or more MCMs were recorded in 75 out of 1,742 (4.3%) pregnancies exposed to ASM monotherapy, as opposed to 21 out of 317 (6.6%) pregnancies exposed to ASM polytherapy (Table 8).

Table 8. Pathological outcomes by ASM treatment categories.
(In this table, 108 spontaneous abortions have been excluded from the denominator).

	No ASM	%	Monotherapy	%	Polytherapy	%	Total
MCM	**1**	3.8	**75**	4.3	**21**	6.6	**97 (**4.7%**)**
CHR	**0**	0.0	**6**	0.3	**3**	1.0	**9 (**0.4%**)**
Syndromes	**0**	0.0	**3**	0.2	**2**	0.6	**5 (**0.2%**)**
No pathological outcome	**25**	96.2	**1,658**	95.2	**291**	91.8	**1,974 (**94.7%**)**
Total	**26**	100	**1,742**	100	**317**	100	**2,085 (**100%**)**

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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 over the years by donations to EURAP from Accord Healthcare Ltd, Angelini Pharma, Bial, Ecupharma srl, Eisai Pharmaceuticals, GlaxoSmithKline, Glenmark Pharmaceuticals, GW/Jazz Pharmaceuticals, Janssen-Cilag, Johnson & Johnson, Krka, Novartis, Pfizer, Sanofi, S.F Group, Teva, UCB biopharma and Zentiva. In addition, national and regional networks may receive support from the same or other pharmaceutical companies.

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