

Congenital malformations in the offspring of women with epilepsy: a two-decade experience in Poland

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SUMMARY

Introduction. The potential for prenatal exposure to antiseizure medications to increase the risk of congenital malformations has been a concern for decades. This study fills an information gap regarding congenital malformations and related factors in the offspring of mothers with epilepsy in Poland.

Materials and methods. The study uses prospectively collected data from an institutional database of a tertiary epilepsy centre between 2000 and 2024, including data from 1,467 pregnancies (mean maternal age = 29.02).

Results. These pregnancies resulted in live births (83.9%), miscarriages (15.4%), and perinatal deaths (0.7%). Major congenital malformations (MCM), identified at birth, were observed in 6.4% of children, most commonly affecting the cardiovascular system (33.0%), urogenital system (21.3%), and involving multiple defects (13.8%). Mothers of children with MCM were older than those of children without MCM, $p = 0.026$. No statistically significant associations were found between the occurrence of MCMs and the type of epilepsy, folic acid intake prior pregnancy, seizures in the first trimester, type of treatment (mono- vs polytherapy), or treatment versus no treatment. Among all medications, only valproate use was associated with a higher risk of MCM – 30.9% versus 20.5%, $\chi^2 = 5.60$, $p = 0.026$, $\phi = 0.06$.

Conclusions. The use of valproate by women with epilepsy during pregnancy increases the risk of birth defects in the child. These findings support efforts to reduce VPA use during pregnancy and to encourage pregnancy planning. Mothers of children with major congenital malformations were statistically older – a weak but potentially clinically significant risk factor. Aside from maternal age, no other analysed factors were linked to a higher risk of malformations.

Key words: women with epilepsy • pregnancy • major congenital malformations • antiseizure medications

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders, affecting approximately 0.3–0.5% of women of childbearing age. During pregnancy, it presents significant challenges due to potential complications from epileptic seizures and the teratogenic risks associated with antiseizure medications (ASMs), espe-

cially in cases of polytherapy and use of valproic acid (VPA) (Vajda et al., 2024; Battino et al., 2024).

Current research shows that the use of certain ASMs, especially VPA, increases the risk of birth defects, mainly affecting the cardiovascular and central nervous systems. Understanding how specific factors – including

the type of epilepsy, medication regimen, and folic acid intake – impact pregnancy outcomes and foetal development is therefore essential for optimising perinatal care in women with epilepsy (Vajda et al., 2023).

The aim of the study was to analyse the risk of major congenital malformations in offspring of women with epilepsy (WWE) in the years 2000 to 2024 in Poland. The analysis included variables such as type of epilepsy (focal vs generalised), folic acid intake prior to pregnancy, presence of tonic-clonic seizures during the first trimester, treatment mode (none, monotherapy, polytherapy), medications used, and their dosages.

MATERIAL AND METHODS

This study is based on a database that prospectively followed WWE pregnancies at the outpatient tertiary Epilepsy Centre in Warsaw, Poland. Data was recorded throughout pregnancy using a standardised form created in 2000 and stored in an electronic institutional database. Between 2000 and December 2024, 1801 WWE pregnancies were entered into the database. The study's inclusion criteria were consecutive pregnant women with an established diagnosis of epilepsy who gave birth, had regular once-per-trimester clinical follow-ups, and were willing to participate. More details on the database, including the inclusion and exclusion criteria, were described in our previous article (Majkowska-Zwolińska and Jędrzejczak, 2022). After excluding 334 WWE who lost to follow-up, the study comprised data on 1,467 pregnancies.

Major congenital malformations (MCM) were defined according to the EURAP (Battino et al., 2024) protocol, based on standardised international criteria, EUROCAT (Eurocat, 1984), and ICD-9 (2024). Only structural anomalies of clinical significance detected at birth were included. Since the teratogenic effect is practically limited to the first trimester and is dose-dependent, we considered the use and dosage of ASM during the first trimester only. Data on treatment were categorised as no drug use, monotherapy (if one ASM was used), or polytherapy (if two or more ASMs were used). The analysis included variables such as type of epilepsy (focal vs generalised), folic acid intake prior to pregnancy, presence of tonic-clonic seizures during the first trimester, mode of treatment (none, monotherapy, polytherapy), medications used, and their dosages. Patients were informed of the study's purpose and the anonymisation of their data. They were assured that

medical treatment decisions were independent of their consent to participate or not. Written or oral informed consent was obtained from all participants. The local ethics committee approved the study (Centre of Postgraduate Medical Education, Warsaw, Poland, approval number 124/PB/2019). IBM SPSS Statistics for Windows, version 29.0, was used for data organisation and statistical analysis. A chi-square test was used to evaluate the association between major congenital malformations and qualitative variables (epilepsy type, treatment mode, folate intake). Student's t-test and Mann-Whitney U test were used to compare maternal age and drug doses between groups (with vs without MCM). Effect size measures calculated include ϕ , V-Cramér, Cohen's d , and r coefficient.

Characteristics of the study sample

The analysis includes 1,467 pregnancies in women with epilepsy, ending between 2000 and December 2024. The patients' ages ranged from 17 to 48 years ($M = 29.02$; $SD = 4.97$). Table 1 presents the frequency of variables related to the type of epilepsy, folic acid intake prior to pregnancy, the occurrence of tonic-clonic seizures during the first trimester, treatment, pregnancy outcomes, the sex of the children, and the presence and type of malformations in children. All percentages are presented as valid percentages, which exclude missing data. Thirteen twin pregnancies were recorded, yielding data on 1,480 children. Among the children, 51.1% were boys and 48.9% were girls. Descriptive statistics for the week of delivery, Apgar scores, and the child's length and weight are presented in Table 2.

RESULTS

Use and dosage of ASMs and the most common drug combinations

The usage frequency of ASMs and basic descriptive statistics of their dosage – mean, minimum, and maximum – are presented in Table 3. For medications used at least 10 times, the standard deviation was calculated.

An analysis of individual ASM usage showed that the most frequently used medications in the sample were lamotrigine (LTG), VPA, and carbamazepine (CBZ), collectively accounting for over 67% of all ASMs. LTG was the most common (26.9%), with an average daily dose of 248.43 mg ($SD = 121.37$). The study also examined the most prevalent drug combinations, observed in at least five patients (Table 4).

Table 1. Frequency of variables associated with epilepsy, pregnancy, and treatment

		N	%
Type of epilepsy	Focal	938	63.9%
	Generalised	529	36.1%
Folic acid intake prior conception (percentages without missing data)	Yes	841	61.4%
	No	528	38.6%
Tonic-clonic seizures in the first trimester (percentages without missing data)	Yes	157	10.9%
	No	1286	89.1%
Mono/polytherapy in the first trimester	No treatment	196	13.4%
	Monotherapy	1014	69.1%
	Polytherapy	257	17.5%
Termination of pregnancy dependent on the gestational week	Early miscarriage	209	14.2%
	Late miscarriage	16	1.1%
	Premature birth	102	7.0%
	Full-term birth	1137	77.5%
	Post-term birth	3	0.2%
Pregnancy outcome	Live births	1231	83.9%
	Spontaneous miscarriage	185	12.6%
	Induced miscarriage	41	2.8%
	Perinatal death	10	0.7%
MCM	No	1373	93.6%
	Yes	94	6.4%
MCM type	Multiple malformations	13	13.8%
	Cardiovascular system	31	33.0%
	Urogenital system	20	21.3%
	Nervous system	7	7.4%
	Musculoskeletal system	9	9.6%
	Cleft palate	5	5.3%
	Eye-ear-face	3	3.2%
	Digestive system	1	1.1%
	Other non-specific	5	5.3%

MCM – major congenital malformation

Table 2. Descriptive statistics of quantitative variables associated with pregnancy and the child

Variable	M	Me	SD	Min.	Max.
Week of delivery – entire sample	34.15	39.00	10.91	3.00	48.00
Week of delivery – live births	38.74	39.00	2.01	25	48
Apgar – entire sample	9.51	10.00	1.14	1	10
Apgar – live births	9.51	10.00	1.13	1	10
Length – entire sample	53.57	54.00	3.72	26.00	68.00
Length – live births	53.69	54.00	3.56	26.00	68.00
Weight – entire sample	3271.70	3280.00	553.07	440.00	4860.00
Weight – live births	3295.01	3300.00	525.51	450.00	4860.00

M – mean, Me – median, SD – standard deviation

Table 3. ASM usage frequency and descriptive statistics of their doses

	N	%	M	SD	Min.	Max.
LTG	416	26.90%	248.43	121.37	25.00	700.00
VPA	311	20.10%	830.52	400.32	150.00	2500.00
CBZ	311	20.10%	761.16	355.27	50.00	1800.00
LEV	230	14.90%	1792.17	798.96	200.00	4000.00
OXC	135	8.70%	1109.44	502.07	75.00	2700.00
TPM	77	5.00%	216.56	114.32	25.00	500.00
GBP	14	0.90%	1642.86	848.27	400.00	3600.00
VGB	10	0.60%	2125.00	489.47	1500.00	3000.00
LCM	9	0.60%	322.22		100.00	400.00
PHT	8	0.50%	264.29		50.00	700.00
TGB	5	0.30%	27.00		15.00	30.00
CLN	5	0.30%	2.50		0.50	6.00
PB	4	0.30%	70.00		30.00	100.00
ESM	4	0.30%	625.00		500.00	1000.00
BNZ	1	0.10%	6.00		6.00	6.00
BRI	1	0.10%	300.00		300.00	300.00
BZN	1	0.10%	5.00		5.00	5.00
CNB	1	0.10%	300.00		300.00	300.00
PGB	1	0.10%	300.00		300.00	300.00
PRM	1	0.10%	250.00		250.00	250.00

The doses of ASMs are measured in milligrams. Each WWE was recorded each time she received a dose of medication.

N – number of observations, M – mean, Me – median, SD – standard deviation

LTG – lamotrigine, VPA – valproate, CBZ – carbamazepine, LEV – levetiracetam, OXC – oxcarbazepine, TPM – topiramate, GBP – gabapentin, VGB – vigabatrin, LCM – lacosamide, PHT – phenytoin, TGB – tiagabine, CLN – clonazepam, PB – phenobarbital, ESM – ethosuximide, BNZ – benzodiazepine, CNB – cenobamate, PGB – pregabalin, PRM – primidone

Association between epilepsy type, folic acid intake, tonic-clonic seizures, and therapy type with the occurrence of malformations in children

The occurrence of major malformations in children was not linked to any of these variables (Table 5). The results were not statistically significant in each case.

The maternal age and the occurrence of congenital malformations in children

The mothers of children with malformations differed in age from those without malformations. Mothers of children with MCM were older (mean age 30.12 ± 5.11) than mothers of children without MCM (mean age 28.95 ± 4.96), $p = 0.026$. The difference was statistically significant, but the effect size was small ($d = 0.24$).

ASM use and major congenital malformations

A key aspect of the study was to examine how the type and dosage of ASM impact the risk of foetal malformations in offspring. The analysis focused on the six most commonly used ASMs. The chi-square test results

Table 4. The most common drug combinations

Drug combinations	N	%
LTG with VPA	42	2.9%
LEV with LTG	36	2.5%
CBZ with VPA	20	1.4%
CBZ with LTG	18	1.2%
CBZ with LEV	14	1.0%
LEV with OXC	12	0.8%
LEV with VPA	10	0.7%
LTG with TPM	10	0.7%
TPM with VPA	9	0.6%
LTG with OXC	8	0.5%
OXC with TPM	7	0.5%
CBZ with TPM	6	0.4%

LTG – lamotrigine, VPA – valproate, CBZ – carbamazepine, LEV – levetiracetam, OXC – oxcarbazepine, TPM – topiramate

showed that only valproic acid (VPA) was significantly associated with an increased risk of MCM ($\chi^2 = 5.60$; $p = 0.026$; $\phi = 0.06$). Among children with MCM, 30.9% of mothers used VPA, compared to 20.5% in the unaf-

Table 5. Association between epilepsy type, folic acid intake, tonic-clonic seizures, and type of therapy with the occurrence of malformations in children

Variable		No malformations		Malformation		Total		χ^2	<i>p</i>	<i>df</i>	<i>Vc/φ</i>
		<i>N</i>	%	<i>N</i>	%	<i>N</i>	%				
Type of epilepsy	Focal	879	64.1%	59	62.1%	938	63.9%	0.15	0.741	1	0.01
	Generalised	493	35.9%	36	37.9%	529	36.1%				
	Total	1372	100.0%	95	100.0%	1467	100.0%				
Folic acid intake prior conception	Yes	787	61.5%	54	60.0%	841	61.4%	0.08	0.823	1	<0.01
	No	492	38.5%	36	40.0%	528	38.6%				
	Total	1279	100.0%	90	100.0%	1369	100.0%				
Tonic-clonic seizures in the first trimester	Yes	150	11.1%	7	7.6%	157	10.9%	1.09	0.386	1	0.03
	No	1201	88.9%	85	92.4%	1286	89.1%				
	Total	1351	100.0%	92	100.0%	1443	100.0%				
Mono/polytherapy in the first trimester	No treatment	189	13.8%	7	7.4%	196	13.4%	3.27	0.195	2	0.05
	Monotherapy	945	68.9%	69	72.6%	1014	69.1%				
	Polytherapy	238	17.3%	19	20.0%	257	17.5%				
	Total	1372	100.0%	95	100.0%	1467	100.0%				

For 2 × 2 tables, ϕ was calculated, whereas for larger tables, *Vc* was used.

N – number of observations, χ^2 – indicates the chi-square test result, *p* – shows the level of statistical significance, ϕ/Vc – reflects the effect size.

Table 6. ASM use and major congenital malformations (MCMs)

Use of ASM		No MCM		MCM		Total		χ^2	<i>p</i>	<i>df</i>	ϕ
		<i>N</i>	%	<i>N</i>	%	<i>N</i>	%				
LTG	No	984	71.7%	67	71.3%	1051	71.6%	0.01	0.906	1	<0.01
	Yes	389	28.3%	27	28.7%	416	28.4%				
	Total	1373	100.0%	94	100.0%	1467	100.0%				
VPA	No	1091	79.5%	65	69.1%	1156	78.8%	5.60	0.026	1	0.06
	Yes	282	20.5%	29	30.9%	311	21.2%				
	Total	1373	100.0%	94	100.0%	1467	100.0%				
CBZ	No	1084	79.0%	73	77.7%	1157	78.9%	0.09	0.794	1	<0.01
	Yes	289	21.0%	21	22.3%	310	21.1%				
	Total	1373	100.0%	94	100.0%	1467	100.0%				
LEV	No	1156	84.2%	81	86.2%	1237	84.3%	0.26	0.769	1	0.01
	Yes	217	15.8%	13	13.8%	230	15.7%				
	Total	1373	100.0%	94	100.0%	1467	100.0%				
OXC	No	1246	90.8%	86	91.5%	1332	90.8%	0.06	1.000	1	<0.01
	Yes	127	9.2%	8	8.5%	135	9.2%				
	Total	1373	100.0%	94	100.0%	1467	100.0%				
TPM	No	1303	94.9%	87	92.6%	1390	94.8%	0.98	0.334	1	0.03
	Yes	70	5.1%	7	7.4%	77	5.2%				
	Total	1373	100.0%	94	100.0%	1467	100.0%				

ASM – antiseizure medication, *N* – number, χ^2 – chi square test, *p* – level of statistical significance, ϕ – the effect size

LTG – lamotrigine, VPA – valproate, CBZ – carbamazepine, LEV – levetiracetam, OXC – oxcarbazepine, TPM – topiramate

affected group. The distribution of MCM types was similar in children of mothers who took and did not take VPA. For the other drugs — LTG, CBZ, levetiracetam (LEV), oxcarbazepine (OXC), topiramate (TPM) — no

significant link was found between their use and congenital malformations (Table 6). Furthermore, no significant differences in dosage were observed between the MCM and non-MCM groups, based on both average

Table 7. The dose of ASM taken and the occurrence of major congenital malformations (MCMs)

ASM dose			M	SD	M	SD	Z	p	r
LTG	No MCM (N = 386)	MCM (N = 27)							
	206.60	248.38	123.30	212.78	249.07	91.06	−0.26	0.793	0.01
VPA	No MCM (n = 279)	MCM (n = 29)							
	154.53	832.08	405.21	154.21	815.52	355.84	−0.02	0.985	<0.01
CBZ	No MCM (n = 285)	MCM (n = 21)							
	152.60	759.47	0.00	165.74	791.67	0.00	−0.67	0.506	0.04
LEV	No MCM (n = 217)	MCM (n = 13)							
	115.47	1792.40	794.80	116.08	1788.46	900.50	−0.03	0.974	<0.01
OXC	No MCM (n = 127)	MCM (n = 8)							
	68.46	1116.73	507.15	60.69	993.75	423.79	−0.55	0.582	0.05
TPM	No MCM (n = 70)	MCM (n = 7)							
	39.36	217.14	112.17	35.43	210.71	144.23	−0.45	0.651	0.05

ASM – antiseizure medication, N – number of observations, M – mean; SD – standard deviation, Z – test statistic value, p – statistical significance, r – effect size index. LTG – lamotrigine, VPA – valproate, CBZ – carbamazepine, LEV – levetiracetam, OXC – oxcarbazepine, TPM – topiramate

doses and ranks in the Mann-Whitney U test. This suggests that, in this sample, the dose of individual drugs did not significantly influence teratogenic risk, which may imply that risk relates more to drug type than to dose, particularly for VPA (Table 7).

An analysis of the relationship between the number of ASMs taken and the occurrence of MCMs showed no statistically significant differences between treated and untreated patients, nor between groups using monotherapy and polytherapy. Furthermore, no correlation was found between specific drug combinations and the incidence of MCM, even in cases involving combinations of any drug with VPA. The VPA dose (≤ 600 mg vs > 600 mg) was not associated with an increased risk of MCM.

MCMs occurred similarly in the live birth and miscarriage groups ($\chi^2 = 0.00$, $p = 1.000$).

DISCUSSION

A long-term study spanning over 20 years investigated the occurrence of congenital malformations in newborns of mothers with epilepsy. This study fills the information gap on MCM and related factors in Poland. The percentage of malformations was higher than in the last EURAP report of May 2025 (6.4% vs 4.5%) (EURAP report), especially since the observations of children in our material are less than 1 year. However, direct

comparisons are not possible, mostly due to methodological reasons. Yet, the distribution of malformations is similar, primarily affecting the cardiovascular and urogenital systems, and multiple systems are involved.

No links were identified between epilepsy type, treatment mode, folate intake, seizure occurrences, and the presence of MCM. However, a weak yet significant correlation between maternal age and MCM suggests that there may be additional age-related risk factors. This finding aligns with existing literature suggesting maternal age as a risk factor for congenital malformations (Ahn et al., 2022; Vajda et al., 2021). However, it should be emphasised that age alone was not a decisive factor – it may instead have an indirect or modulatory role in the relationship between pharmacological therapy and foetal development.

Our analysis reaffirmed previous findings regarding VPA's teratogenicity (Tomson, Battino, 2018; Tomson, Battino, 2019). The substantial use of VPA and CBZ in our material (each accounting for 20.1%) highlights their ongoing role in treatment, despite their known teratogenic risks, particularly with VPA.

The absence of a dose-dependent relationship between VPA and MCM indicates that even lower doses might be risky or that the sample size was too small to detect differences. These findings support clinical guidelines to avoid VPA during reproductive years and

the first trimester, to prefer monotherapy with the lowest teratogenic risk, and to plan folic acid supplementation before pregnancy. Although folic acid did not show a protective effect in this study, as well as in other studies (Pack et al., 2024 Vajda et al., 2022), planning remains vital.

Surprisingly, we did not confirm the established link between polytherapy and an increased risk of birth defects. Earlier research, Morrow et al. (2006), Tomson and Battino (2009), and Meador et al. (2008), clearly demonstrated that using more than one ASM, especially those containing valproate, significantly raises the risk of developmental malformations, primarily neural tube defects, heart defects, and cleft palate. These findings have led to recommendations for monotherapy, when possible, as a safer approach for the foetus. Considering these reports, the current study's results, which did not show a notably higher rate of congenital malformations with polytherapy, are probably due to the limited sample size and possibly underestimating MCMs detected after the neonatal period.

Furthermore, recent studies (Weston et al., 2016) indicate that, with appropriate drug choices, even polytherapy does not necessarily carry a significantly higher risk of defects. This emphasises the need for a nuanced approach – considering not only the number of medications but also their specific combinations, dosages, and potential interactions.

Considering the evolution in clinical practice over more than twenty years, there have been significant shifts in how epilepsy among women of childbearing age is managed. These include avoiding the most teratogenic drug combinations and using lower doses, which may diminish the risk of MCMs in the future. An analysis of anti-seizure medication use among women of childbearing age in Poland over two decades showed a clear increase in the use of medications with safer pharmacokinetics and lower teratogenic potential (Jędrzejczak and Majkowska-Zwolińska, 2025). Newer ASMs, such as lamotrigine and levetiracetam, are linked with a more favourable safety profile during pregnancy compared to older drugs like valproate (Vajda et al, 2010; Meador et al., 2018; Tomson et al., 2018; Meador et al., 2013).

CONCLUSIONS

The use of valproic acid by women with epilepsy during the first trimester of pregnancy increases the risk of birth defects in the child. Mothers of children with

major congenital malformations were statistically older – this is a weak but potentially clinically significant risk factor. No other analysed factors (such as the type of epilepsy, mode of treatment, VPA dose, presence of seizures in the first trimester, or folic acid intake) were linked to a higher risk of malformations. The findings endorse the aim of decreasing VPA use during pregnancy and encouraging pregnancy planning.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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