Preventing Teratogenicity in Women with Epilepsy

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Abstract

Over the last 50 years there has been a significant increase in our understanding of the issues faced by women with epilepsy, in both planning and undertaking pregnancy. The risks of teratogenicity associated with antiseizure medications have emerged slowly. The major pregnancy registers have substantially contributed to our knowledge about teratogenic risk associated with the commonly used antiseizure medications. However, there are substantial gaps in our knowledge about the potential risks associated with many third-generation drugs. The remit of the pregnancy registers and the wider research focus has moved beyond anatomical major congenital malformations. Increasingly neurodevelopmental and behavioral abnormalities have been investigated after in utero exposure to antiseizure medications. Public health approaches can help reduce the risk of teratogenicity. However, neurologists still have a vital role in reducing the risk of teratogenicity at an individual level for women attending their clinic. They also have responsibility to ensure that women with epilepsy are aware of the rationale for the different available options.

Keywords
- pregnancy
- reproduction
- seizures
- valproate
- malformation
- neurodevelopment

The last 50 years has seen an increasing focus on the health of women with epilepsy during pregnancy and the effect of seizures and antiseizure medications (ASMs) on the unborn baby. However, this knowledge has been acquired only painfully slowly. Until the 1970s there was almost no research into the safety of ASMs in pregnancy.[1] In many ways, this was one expression of the stigma and discrimination faced by women with epilepsy. It is not so long ago that women with epilepsy were ostracized from civic society and encouraged not to have children. This situation is changing with greater societal acceptance and integration of those with neurological conditions such as epilepsy. The current expectation is that women and girls with epilepsy will be assessed before pregnancy to optimize their care, will be fully informed of the benefits and risks of different decisions, and will have access to specialist expertise as required.[2]

Approximately one quarter of all people with epilepsy are women of child-bearing potential, for whom these issues are real-world practical concerns.[2] Up to 0.5% of all pregnancies are in women with epilepsy.[3] In the United States, 25,000 children are born each year to the 1.3 million women with epilepsy in their reproductive years.[4] The widespread use of ASMs beyond epilepsy indications is of concern, and it is essential that all prescribers are appropriately aware of the teratogenic risks.[5]

Women with epilepsy generally need to continue ASMs during pregnancy to reduce the chance of having seizures, given their physical, psychological, and social consequences. Thus, ASMs are a common potential iatrogenic teratogen.[6] Teratogenicity comprises both anatomical major congenital malformations (MCMs) and neurodevelopmental aberrations.[7] Examples of common MCMs with ASMs include cardiac defects, cleft-palate disorders, as well as neural tube defects, but sometimes also intrauterine growth restriction and minor congenital malformations. Polygenic variables modify the risk, through complex interaction with environmental factors such

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Table 1 The time-sensitive nature of teratogenic exposures resulting in specific patterns of malformations

Weeks of gestation											
1	2	3	4	5	6	7	8	9	16	32	38
Not vulnerable to teratogenicity, but may suffer fetal loss		Neural tube defects, cognitive and neurodevelopmental defects									
			Cardiac defects, including ASD, VSD								
			Upper limbs								
				Lower limbs							
					Cleft lip						
				Low set ears and deafness							
						Cleft palate					
							Genital abnormalities				

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect.
Note: Times indicated represent the most sensitive times for teratogenic exposures (for more detailed, see "Human birth defects[18])

as dose and duration of teratogenic exposure. Malformations from first trimester exposure generally need medical, surgical, or cosmetic intervention in early life.[8] In severe cases, teratogens cause fetal loss. The consequences of these drug exposures can alter an individual's life course and result in potentially avoidable disability and reduced life opportunities. They have consequences for the individual, the family, and for wider society. Other factors may also influence the risk of major malformations in babies born to women with epilepsy, including maternal smoking, use of recreational drugs, maternal diabetes glycemic control, obesity, nutritional deficiencies, genetic factors, other drug exposures, and infections.[9]

The embryological development of the human fetus involves a complex set of genetic and molecular processes. Teratogens can impact different elements of embryological development at different time points in the process (►**Table 1**) with consequent aberrant outcomes (►**Table 2**).[10–17] By the end of the first trimester, all the major organ systems have formed, but brain development continues throughout pregnancy and into infancy.[18]

Putative mechanisms for teratogenicity include factors related to folate deficiency, ischemia, neuronal alterations, the formation of reactive intermediates (e.g., free radicals and oxidative damage), and neuronal apoptosis.[10,19] The latter mechanism is implicated in aberrant neurodevelopment. Current molecular understanding of ASM teratogenicity has not allowed the development of novel genomic tools for risk prediction, or precision therapies to prevent problems in high-risk pregnancies.

The global context of teratogenicity in mothers with epilepsy is important. Around 80% of people with epilepsy live in low- and middle-income countries, often with less robust public health systems.[20] First-generation ASMs such as phenytoin and phenobarbital are frequently used and more modern drugs are less available. We urgently need global approaches to target teratogenicity. Around 1 million people take valproate across the world.[21] In the United States, approximately 341,000 women of reproductive potential (aged 13–45 years) take valproate, with around 10% being for an epilepsy indication.[22]

Table 2 Summary of findings from preclinical studies involving animal studies for the most commonly used ASMs[10–17]

Antiseizure medication	Malformations noted in animal studies
Carbamazepine	Cardiac defects, cleft palate, gastroschisis, hydrocephaly, hydronephrosis, skeletal defects
Lamotrigine	Cleft palate, exencephaly, midfacial hypoplasia, skeletal defects, urogenital abnormalities
Levetiracetam	Minor skeletal defects
Phenobarbital	Cardiac abnormalities, cerebral ventricular enlargement, cleft palate, hydronephrosis, skeletal ossification disorders, urogenital abnormalities
Phenytoin	Cleft disorders, cardiac defects, cerebral ventricular enlargement, digital defects, skeletal ossification delay, renal abnormalities (including hydronephrosis), ocular abnormalities
Topiramate	Craniofacial, limb malformations and skeletal ossification defects
Valproate	Cardiac abnormalities, craniofacial and skeletal defects, exencephaly and neural tube defects, urogenital

Abbreviation: ASM, antiseizure medication.

In this review, we outline the historical background to our understanding of increased teratogenic risk—causing congenital malformation and neurodevelopmental dysfunction—with some ASMs. We outline the current state of the evidence and focus on malformation data from the major pregnancy registers, noting their limitations but also their legacy and future. We advance projections for how this field might progress and the strategies that might help prevent teratogenicity. We also outline gaps in current knowledge that might help women with their decisions around medication.

Historical Development of Our Understanding of Risk of ASMs

Pregnant women have historically been excluded from clinical trials, attempting to uphold the ethical principle of "first do no harm," yet ironically slowing the accumulation of knowledge about drug safety. Identifying thalidomide as a potent teratogen in the early 1960s raised the profile of prescribing in pregnancy and led to increased regulatory conditions for drug use.[23] The lessons learned were relevant to the epilepsy community, and by 1963, the first concern over an ASM was published when a child of a mother taking an ASM was born with microcephaly, cleft disorder, gastrointestinal problems, and low IQ.[24] Soon after, a retrospective study from west Germany including 426 pregnancies from 246 women with epilepsy provided reassurance of the safety of ASMs in pregnancy, reporting an MCM rate of 2.2%, similar to the background population.[25]

However, further teratogenicity cases emerged slowly during the 1960s.[1] In 1968, an influential letter to an editor reported six children with cleft disorders, four with cardiac defects, and dysmorphic appearance.[26] This pattern resembled that in children affected by antifolate drugs, leading to a proposed mechanism for ASM teratogenicity. By the early 1970s, several large studies had reported increased MCM risk associated with epilepsy compared with control populations, although these studies did not give due consideration to confounders including age, diabetes, and family history of congenital malformations.[1]

By the mid-1970s, standard contemporary textbooks on epilepsy pharmacology were reporting issues related to teratogenicity, such that in 1974 Eadie and Tyrer[27] remarked, "It now must be suspected that anticonvulsants … may occasionally be associated with teratogenic effects" … "the risk of teratogenicity seems to be two to three times that in the general population." They tempered their observations with the comment, "decisive studies are not yet available showing that it is the therapy, rather than the presence of epilepsy, which is responsible for the increased incidence of fetal malformations in the circumstances under consideration." This comment reflected concerns at the time that maternal epilepsy was an important confounding variable. The sense of false confidence in clinical experience was reflected in the statement that "diphenylhydantoin has been used widely for over 30 years and the incidence of its teratogenic effects in man must be low or one might have expected the phenomenon to be more definitely recognized by now."[27] In 1978 Donaldson stated in *Neurology of Pregnancy*[28] that the "possible teratogenic effect of anticonvulsants was not a concern until the thalidomide catastrophe, even though phenobarbital and phenytoin had been in use since 1912 and 1938, respectively." By 1975, Janz had reported that the frequency of orofacial clefts and congenital heart disease was two to four times higher than the background population.[29] Other minor malformations had been increasingly reported in the early 1970s. Observational evidence accumulated over the 1970s and 1980s, and by the 1990s, a standard epilepsy textbook[30] stated, "No antiepileptic drug (AED) can be considered absolutely safe in pregnancy … and that "the weight of evidence tends to support some teratogenic effect of AEDs," although the perceived lack of characteristic patterns of malformations for some drugs was considered to indicate that such drugs were not teratogenic. Some still held that seizure-related consequences were causing MCMs. By 1982, sodium valproate had been linked to an increased risk of spina bifida.[31] Authors in the early 1990s advocated that women taking valproate should be informed of the additional risks of spina bifida. By the 2000s, there was a more detailed understanding of the anatomical and behavioral teratogenicity associated with certain ASMs.[10]

Preclinical animal studies are a routine part of the drug regulatory approval. ►**Table 2** shows the preclinical outcomes of pregnancies exposed to ASM in lower species.[10–17] Based on these data as well as on emerging clinical data, the U.S. Food and Drug Administration (FDA) specified different levels of drug safety in pregnancy.[10–17] Preclinical data for carbamazepine, phenytoin, topiramate, and valproate showed similar types of teratogenic malformation as in humans.[11,15–17] However, lamotrigine, levetiracetam, and oxcarbazepine, despite being considered among the safest in human pregnancy, showed teratogenic effects in animal studies.[12,13,32] Clearly, the best species model to guide human prescribing is human pregnancy.

Global Pregnancy Registries and Post-Marketing Surveillance

In the mid-to-late 1990s, several groups of researchers as well as groups from the pharmaceutical industry established prospective multicenter observational studies, trying to understand better the risks of ASMs in humans using the best permissible study design (►**Fig. 1**).[33–40]

When considering the results of each of the pregnancy registries (►**Table 3**) and in turn making comparisons, it is important to remember each registry study has its own strengths and weaknesses (►**Table 4**).[41] The key concerns are possible enrolment bias and representativeness of real life, but other concerns include nonstandardized data collection across different studies (epilepsy cause, epilepsy syndrome, seizure types); lack of drug concentration measurements as part of the protocols; certain confounders not being assessed; and different approaches to determining outcomes in nonblinded studies.

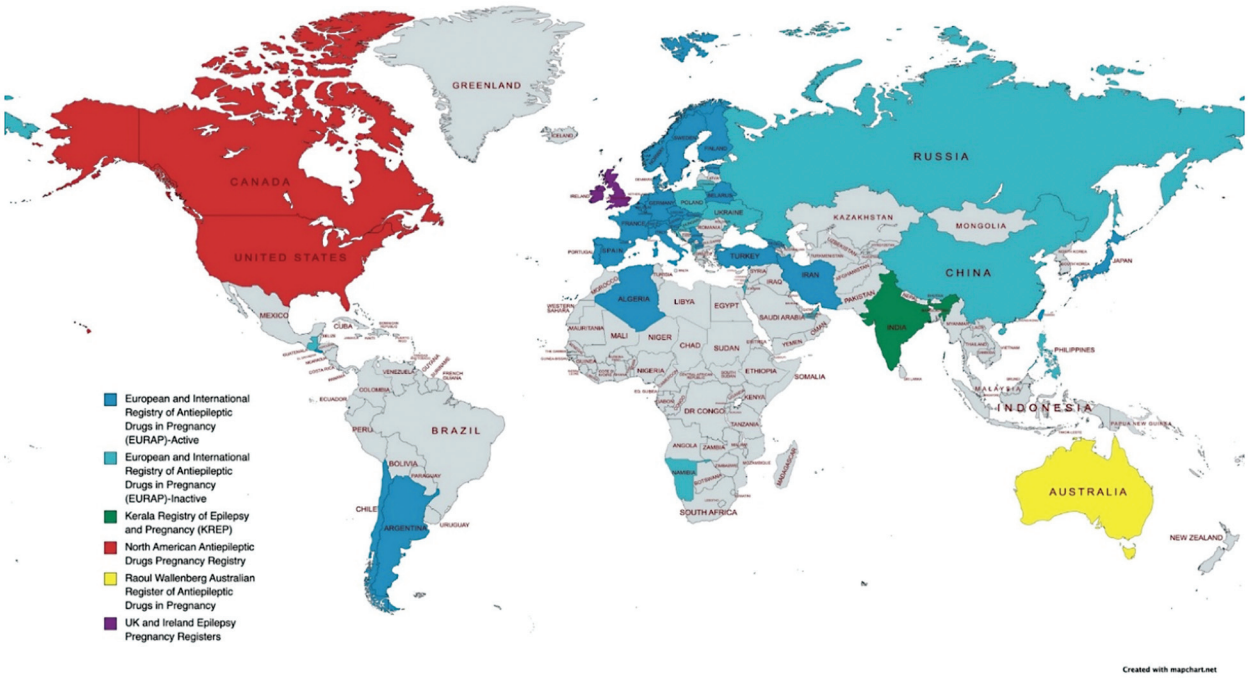

Fig. 1 World map showing countries participating in major registry research.

Previous attempts to harmonize data and to consider how data might be shared between the major registries has generally not progressed.[41] One important exception is the successful collaboration with the European Registry of Antiepileptic Drugs and Pregnancy (EURAP) study, which receives a similar percentage of registrants from some of the other major registries.[38] Unfortunately, individual registry data for many ASMs remain underpowered and unpublished, and methodological differences have so far limited attempts at meta-analysis.

Results of the Pregnancy Registries

The international pregnancy registries have published initial results over the last 15 years. Despite differences in methods, a broad consensus has emerged for the relative risk of malformation with various ASMs.

Babies born to women with epilepsy who took ASMs in pregnancy have a two to three times greater risk of MCM than those born to women without epilepsy.[30] This risk appears to be mediated by ASMs used in the first trimester. Certain factors are associated with this increased risk, including the particular ASM itself—with valproate associated with the highest risk[42] and lamotrigine and levetiracetam associated with the lowest risk.[43] Other factors include the ASM dose and exposure to polytherapy[44] rather than monotherapy (there are exceptions to this rule); the risk potentially increases with a larger number of ASMs used.[6] However, the particular epilepsy syndrome and having seizures during pregnancy were not associated with MCM. There are clear genetic modifiers that impact on risk of teratogenic outcome.[45] Women whose first child had an ASM-associated major malformation have an increased risk of this in further pregnancies, compared with those women whose first child had no malformation.

Women with epilepsy need to have the results of the major registry studies and their implications presented to them in an understandable and useful format, shaped to their individual needs. The sharing of information about teratogenic risk should occur in the context of a woman's wider information needs and with an individualized assessment of their baby's risk of teratogenicity. It is essential to prepare for this early, including before, during, and after pregnancy (see ►**Table 5**).

Monotherapy

Lamotrigine

The Cochrane review (2016)[43] found that the MCM risk with lamotrigine was similar to that of the background population. The North American AED Pregnancy Registry[46] (NAAPR) reported a 10-fold higher rate of cleft palate following in utero exposure to lamotrigine. However, the population-based European Surveillance of Congenital Anomalies (EUROCAT) database,[47] collecting congenital malformation data from 14 European countries, found no association with lamotrigine and orofacial clefts.

The EURAP study reported a dose-related increase in the MCM rate associated with lamotrigine with a daily dose above 325 mg.[38]

Levetiracetam

Reassuring evidence to date regarding levetiracetam's MCM risk has led to it fast becoming one of the most used ASMs in

Table 3 Major congenital malformation (MCM) risks reported by large international registries

	MCMs reported by pregnancy registries by ASM exposure					
	UK and Ireland Epilepsy and Pregnancy Register	International Registry of Antiepileptic Drugs and Pregnancy or EURAP		North American AED Pregnancy Registry	Kerala Registry of Epilepsy and Pregnancy (KREP)	Raoul Wallenberg Australian Pregnancy Register
Antiseizure medication	Number of MCM in monotherapy exposures/total number of monotherapy exposures (MCM rate; 95% CI)					
Carbamazepine	43/1,657 (2.6%; 1.9–3.5) Dose data	Dose ≤700 mg	58/1,276 (4.5%; 3.5–5.8)	31/1,033 (3.0%; 2.1–4.2)	23/490 (4.7%; 2.8–6.6)	
		>700 mg	49/681 (7.2%; 5.4–9.4)			24/409 (5.9%)
Lamotrigine	49/2,098 (2.3%; 1.8–3.1 Dose data	Dose ≤ 325 mg	46/1,870 (2.5%; 1.8–3.3)	31/1,562 (2.0%; 1.4–2.8)	1/50 (2.0%; −1.8 to 5.9)	20/406 (4.9%)
		>325 mg	28/644 (4.3%; 2.9–6.2)			
Levetiracetam	2/304 (0.70%; 0.2–2.5)	17/599 (2.8%; 1.7–4.5)		11/450 (2.4%;1.2–4.3)	5/106 (4.7%; 0.7–8.8)	5/139 (3.6%)
Oxcarbazepine	Not reported	10/333 (3.0%; 1.4–5.4)		4/182 (2.2%; 0.6–5.5)	5/71 (7.0%; 1.1–13.0)	1/19 (5.3%)
Phenobarbital	Not reported	19/294 (6.5%; 4.2–9.9)		11/199 (5.5%; 2.8–9.7)	8/137 (5.8%; 1.9–9.8)	0/2 (0%)
Phenytoin	3/82 (3.7%; 1.3–10.2)	8/125 (6.4%; 2.8–12.2)		12/416 (2.9%; 1.5–5.0)	7/119 (5.9%; 1.7–10.1)	1/44 (2.3%)
Topiramate	3/70 (4.3%; 1.7–13.3)	6/152 (3.9%; 1.5–8.4)		15/359 (4.2% (2.4–6.8)	Not reported	1/53 (1.9%)
Valproate	82/1,220 (6.7%; 5.5–8.3) Dose data	Dose ≤650 mg	38/600 (6.3%; 4.5–8.6)	30/323 (9.3%; 6.4–13.0)	27/341 (7.9%; 5.1–10.8)	43/290 (14.8%)
		>650 to ≤1,450 mg	75/666 (11.3%; 9.0–13.9)			
		>1,450 mg	29/115 (25.2%; 17.6–34.2)			
Zonisamide	3/26 (13.0%; 4.5–32.1)			0/98 (0%; 0.0–3.3)		1/6 (with one spontaneous abortion)

Abbreviation: ASM, antiseizure medication.

reproductively active women.[48] The risk of levetiracetam overlaps with the background level of risk of malformation.[43]

The UK registry identified two MCMs with levetiracetam among 304 monotherapy cases.[34] Similarly, EURAP and the NAAPR found low rates of MCMs, 2.8 and 2.4%, respectively.[37,38] Of note the UCB Pharma Levetiracetam registry reported an overall risk of 10.4% (from 46 cases among 444 live births), although the inclusion factors and methods differed in this study and substantially altered the findings.[49] To date, no registry has reported a dose-related increase in MCM associated with levetiracetam.

Carbamazepine

The EURAP study[38,50] reported a higher MCM rate with carbamazepine than the background population with a dose-related increase in MCM rate. For those receiving less than 400 mg/day, the MCM rate was 3.4%; the rate was higher for those using between 400 and 1,000 mg/day, but it was highest for those taking over 1,000 mg/day, with an MCM rate of 8.7%.

In utero carbamazepine use was initially linked to spina bifida.[51,52] Cardiac abnormalities, cleft disorders, skeletal malformations, and urological abnormalities including hypospadias have all been reported.[7]

Sodium Valproate

There is now an international consensus that valproate is a potent teratogen.[53] The first reports of its teratogenicity came in the early 1980s with concerns about associations with spina bifida.[54–57] By 1984, a constellation of phenotypic and dysmorphic features was termed "fetal valproate syndrome."[58] In fact, several fetal ASM syndromes were identified associated with major malformations and developmental cognitive difficulties including phenytoin and carbamazepine.[59,60] However, many features of these syndromes overlap, and their individual features are not so specific for a particular ASM.

Across prospective large-scale studies, valproate has the highest MCM risk in exposed offspring, with an approximate 10% risk of anatomical teratogenicity. The risk is dose-dependent. The EURAP study found a 5.6% risk of MCM among pregnancies of women taking less than 700 mg of valproate per day, a 10.4% risk when taking 700 to 1,500 mg per day, and 24.2% when taking over 1,500 mg/day.[38] The most common malformations associated with valproate included cardiac defects and hypospadias, each of which was found in 2% of infants exposed to valproate; cleft lip, gastrointestinal, renal, neural-tube defects, and digital abnormalities have all been reported.[53]

Table 4 Global contribution from different countries, listed as enrolling in the different major international epilepsy and pregnancy registers

Registry	North American AED Pregnancy Registry	UK and Ireland Epilepsy and Pregnancy Register	International Registry of Antiepileptic Drugs and Pregnancy EURAP	Kerala Registry of Epilepsy and Pregnancy (KREP)	Raoul Wallenberg Australian Pregnancy Register
Design	Prospective (enrolled before prenatal screening)/retrospective	Prospective	Prospective (enrolled before prenatal screening and within week 16)/retrospective	Prospective	Prospective (enrolled before prenatal screening)/retrospective
Location	United States and Canada	United Kingdom and Ireland	International collaboration of >40 countries	Kerala, India	Australia
Enrolment process	Self-enrolment by women	Medical, nursing and self-enrolment	Medical	Medical and self-enrolment	Self-enrolment
Inclusion/exclusion criteria	Women using ASM in pregnancy for any indication	Women with epilepsy on ASMs or not using ASMs in 1st trimester. Prenatal tests with abnormality before referral, and change in ASM in first trimester were excluded	Pregnant with ASM exposure at conception. Change in ASM in first trimester, or unclassified outcome were excluded	Women with active epilepsy on or not on ASMs, or women with other indications on ASMs in first trimester	Women using ASM in pregnancy for any indication (yet majority epilepsy), and women with epilepsy without ASM use (in the first half of pregnancy)
Diagnostic confirmation	Self-report and records review from neurologist	Patient's doctor	Patient's doctor	Patient's doctor	Patient's doctor
Data collection	Three telephone contacts with patient and supplemented by medical records review	Two contacts with patient's doctor	4–5 contacts, from reports from treating referring physician, supplemented by medical notes	4–5 contacts, from reports with physician, supplemented by medical notes	4 telephone contacts with patient (initial contact, 7 mo, 1 mo postpartum, and 12 mo after) and supplemented by medical records review
Assessment of outcome	Blinded teratologist record review, supplemented with direct contact with doctor/patient as required	Experienced clinical geneticist chart review	Central classification by blinded teratologist based on physician report	From reporting physician report, with echocardiography and ultrasonography surveillance	Based on medical report
Exposures assessment	ASM regimen and dose but not drug levels	ASM regimen and dose but not drug levels	ASM regimen and dose but not drug levels	ASM regimen and dose but not drug levels	ASM regimen and dose but not drug levels
Time to complete assessment	Within 5 d, and then at 8–12 wk	Within 3 mo from birth	Within 12 mo of birth	Within 12 mo of birth	Within 12 mo of birth

Abbreviations: AED, antiepileptic drug; ASM, antiseizure medication.

The UK Registry study found no difference in the risks for malformations between standard-release valproate and controlled-release valproate preparations (relative risk [RR]: 1.11; 95% CI: 0.67–1.83). Similarly, for those exposed to single or multiple daily administrations of valproate, there were no statistically significant differences (RR: 0.99, 95% CI: 0.58–1.70).[61]

Topiramate

The MCM risk for topiramate is between 4.2 and 4.9% for monotherapy.[35,37] Topiramate exposure in utero has been associated with an increased risk of cleft lip, cleft palate, and hypospadias.[62] Topiramate polytherapy carries a high risk; based on data from the Australian Pregnancy Register, the MCM rate is 14.1%, and should ideally be avoided in pregnancy, especially with valproate coprescription.[63]

The North American Registry[64] reported that 17.9% of exposed pregnancies were associated with being small for gestational age (relative risk of 2.4 compared with lamotrigine). The MCM rate with topiramate was 4.2% (15 of 359 monotherapy cases), including a 1.4% rate of oral cleft, which was 10-fold greater than that of their control group (prevalence: 0.11%). The FDA therefore considers topiramate to be a teratogen [Category D, previously Category C [2011]].[16] Preliminary data from the UK registry for topiramate[35] use in first trimester found a 2.2% rate of facial clefts, again a 10-fold increased risk compared with the UK general population risk of 0.2%.

Oxcarbazepine

The recent Cochrane review[43] found a MCM rate of 2.4% (95% CI: 0.9–4.7%) for oxcarbazepine, based on 238 pregnancies from four studies. No studies have looked at dose response. Since the 2016 meta-analysis, the Kerala registry[40] published a concerning signal of possible MCM risk.

Zonisamide

There are few published data for zonisamide. A study from Japan[65] reported two MCMs from 26 pregnancies with zonisamide exposure, giving a rate of 7.7% (both were

Table 5 Practical opportunities for a neurologist to reduce the risk of teratogenicity

Opportunity	Practical advice
Before pregnancy	
Discuss early and often	From the time of pediatric transition, issues related to future pregnancy considerations should be discussed, to include teratogenic risk of particular antiseizure medications (ASMs), appropriate contraception for those of a sexually active age, given the high risk of unplanned pregnancies today. It is important to offer the opportunity to discuss these issues often to allow informed decision-making
Review the diagnosis	Before embarking on pregnancy if there is diagnostic doubt, it is essential to try and secure the diagnosis. If functional seizures are the exclusive seizure type, ASMs should be withdrawn promptly. If functional seizures co-exist with epileptic seizures, consider any scope to reduce medication if dosage had been escalated unnecessarily
Review predisposing triggers	Review lifestyle factors such as alcohol, sleep deprivation, especially for those with idiopathic (genetic) generalized epilepsy. It could be the case that previously medication doses were escalated due to seizure provocation by lifestyle factors. If lifestyle factors are addressed, it may offer an opportunity to reduce the dose of some ASMs
Review syndrome and antiseizure medication choice	Ensure the medication is appropriately matched for the epilepsy syndrome. Choose less teratogenic options where possible. Valproate should be considered only in situations where the benefit may outweigh the risk and this is typically after other options have been tried first. There are some scenarios where a low dose of valproate in polytherapy is safer than high-dose valproate monotherapy in terms of MCM risk. Consider using the lowest possible dose of ASM to control seizures. Acknowledge the uncertain malformation risk related to newer ASMs. Make changes before pregnancy ideally. Dose fragmentation or using extended release preparations have not been shown to reduce malformation rate
Review other lifestyle factors	Review other medications and ask the patient to discuss with their primary care doctor/relevant specialist. Other factors such as obesity, glycemic control in diabetes, alcohol intake, smoking status, illicit drug use should all be addressed as part of a comprehensive assessment of teratogenicity risk
Folic acid supplementation	Optimizing folic acid stores through supplementation is important to minimize risk of neural tube defects and shows some benefit to neurodevelopment. Local guidelines for dose should be used
During pregnancy	
Early access to expertise policy	Ensure that women know to get in touch with your service on an emergent basis and facilitate systems to allow rapid review of such women. This could facilitate dose reduction of ASM or ASM substitution if required
Balanced risk–benefit discussions	Seizure control and avoidance of injury, status epilepticus, and SUDEP need to be balanced with avoidance of teratogenicity and other ASM side effects. Risks of teratogenicity should be discussed specifically, and not simply in general terms. If possible, consider the dose in risk predictions, and if previous children were born with malformations on the same treatment regimen
Research	Woman should be offered the opportunity to contribute to future knowledge by informing them of the relevant pregnancy register in their region
Reassure	For most women with epilepsy, pregnancy results in a healthy baby. Additionally, to date there is no evidence of harm from focal aware seizures, absences, or myoclonic seizures unless the woman sustains an injury. In certain situations, after risk–benefit discussions ASMs may be justifiably not up-titrated, e.g., several myoclonic seizures after a late night where the patient has never had a convulsion
Coordinated care	Care should be shared between an obstetrician and a neurologist, ideally, each with a specific professional interest in the issues of epilepsy and pregnancy. Women should undergo a high-resolution ultrasound scan (at 18–20 weeks of gestation) and follow-up to allow the earliest opportunity for malformation detection
After pregnancy	
Follow-up	Malformations in offspring can become more apparent over the first year of life. Neurodevelopmental concerns may take longer to emerge. It is important for woman to be mindful of this and checking on the ongoing welfare of the child is good clinical practice to allow early engagement with pediatrics where needed
When a malformation has occurred	Where a malformation has occurred on a certain drug regimen, there is evidence of a higher risk of a repeated malformation in future pregnancies. It is especially important in these situations to take a fresh look at options for treatment and make an individualized informed decision

Abbreviations: ASM, antiseizure medication; MCM, major congenital malformation.

polytherapy with valproate and phenytoin combinations). The North American registry[37] reported 90 zonisamide exposures with 0% (95% CI: 0–3.3) MCM rate. However, they subsequently found zonisamide was associated with an increased rate of low birth weight, with 14% of infants being small for gestational age, compared to 7 to 12% with lamotrigine. The UK and Ireland Registry[36] recently reported an MCM rate of 13% (95% CI: 4.5–32.1) for monotherapy zonisamide, based on three cases from 26 exposures. Small numbers clearly limit interpretation. Interestingly, the MCM rate for polytherapy (6.9%, 95% CI: 3.0–15.2) was lower than for monotherapy. Four of five MCMs occurred with valproate and/or topiramate use, but after excluding valproate and topiramate combinations there was only 1 MCM of 55 cases (MCM rate of 1.8% [95% CI: 0.32–9.6]). There are no clear published dose–response data.

Clobazam and Clonazepam

The Kerala study[66] has identified a signal of increased MCM risk after in utero exposure to clobazam, based on two MCM cases from nine pregnancies (MCM rate of 22.2%, 95% CI: 6.3–54.7). A subsequent study[67] from Kerala reported 12 MCMs from 125 polytherapy clobazam exposures (MCM rate of 9.6%), and 3 MCMs from 38 clonazepam polytherapy exposures (MCM rate of 7.9%). A French healthcare database cohort study[68] of 1,886,825 pregnancies identified a signal for microcephaly among 980 exposures to clonazepam.

Lacosamide

There are no available data to make any reliable statements about teratogenic risk with lacosamide.

Perampanel

None of the major pregnancy registries has reported outcomes related to perampanel, and there are too few data to make reliable statements on its MCM risk. However, a recently published report[69] provided some preliminary data. Ninety women underwent 96 pregnancies, with 43 reaching full term, 28 fetal losses, 18 lost to follow-up, and seven were still undergoing ongoing data collection. One of the babies who suffered a stillbirth was noted to have Fallot tetralogy, and one of the live born babies was deaf and had cystic fibrosis.

Phenytoin/Phenobarbital

The Cochrane review reported MCM rates of 6.3% for phenytoin and 7.1% for phenobarbital.[43] The fetal hydantoin (phenytoin) syndrome comprises midfacial hypoplasia, increased risk of cleft lip, hypoplasia of the distal phalanges, small nails, and cardiac defects.[70] Phenytoin has been associated with an increased risk of cleft palate. The North American Registry published data on phenobarbital including five MCM cases from 77 women (MCM rate of 6.5%, 95% CI: 2.1–14.5%). In this series, there was one cleft lip and palate and four cardiac defects.[37]

Gabapentin

The Cochrane meta-analysis[43] identified only 190 in utero exposures to gabapentin, with an MCM prevalence of 1.47% (95% CI: 0.26–3.64). The North American Registry[37] found a nonsignificant outcome when comparing to women not taking gabapentin (RR: 0.61, 95% CI: 0.07–5.18). There was no significant dose response, but the low numbers would make this an underpowered observation.

Polytherapy

Polytherapy combinations are difficult to analyze due to their complexities as well as the vast number of possible combinations. A general dogma is that polytherapy is associated with higher risk of malformation,[42] and particularly regimens with valproate or topiramate.[42,63,67,71–73] Emerging evidence suggests valproate in low dose in polytherapy, rather than high-dose valproate monotherapy,[72] could be an advantageous approach to reduce malformation rate, and retain the efficacy of valproate. A low dose of valproate may be one approach for those with idiopathic (genetic) generalized epilepsy, where valproate appears the best option for a particular woman.[74]

Limitations

Each pregnancy register has its own limitations. One major issue is difficulty with recruitment. Low-level recruitment of women taking the newer ASMs means that it will potentially be decades before there are answers regarding safety. Confounders have not been fully addressed.[75] Issues such as maternal age, alcohol, folate levels, exercise, smoking, obesity, assisted fertility, and how each of these has changed in the control population are important factors to consider when considering how MCM rates have changed longitudinally, in terms of measuring the effect of the pregnancy registers. Significant non–drug-related factors associated with MCM rate in the Australian registry data included use of assisted fertility measures, family history of MCM, and maternal age.[75] Research in this area must adapt to provide a better view of teratogenic outcomes with a longitudinal approach on understanding the long-term impact.

Extension Studies

Although the pregnancy registries were established to determine the relative risks of MCMs, they have extended their remit to study other aspects relating to pregnancy and infant health, including seizure control in pregnancy, the risks of fetal loss, and obstetric outcomes. Working with other research groups and spanning national and international boundaries, those maintaining the registers have studied the effects of ASMs in pregnancy on neurodevelopment, including the effects on cognitive functioning and the risks for autistic spectrum disorder and autism, attention-deficit disorder, and other behavioral problems. Independent research groups have added further information, including the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) and Maternal Outcomes and NEAD (MONEAD) study groups, and those using national surveillance systems, for example, from Scandinavian countries.

These research group results have consistently shown that cognitive functioning is impaired in children born to women

with epilepsy, with valproate having the greatest risk. Perhaps 30 to 40% of all infants exposed to valproate will have lifelong neurodevelopmental disorders, impacting on their educational attainments and needing additional support (**Box 1**: **case history**).[76] As part of this, studies have shown a mean reduction in full-scale intelligence quotient (IQ) of between 8 and 11 points following valproate exposure compared with exposure to other ASMs, as well as increased risks for reduced verbal, nonverbal, memory, and executive functioning.[77] Valproate has also been associated with two- to threefold increased rates of autistic spectrum disorders and autism and attention-deficit hyperactivity disorder.[78,79]

Box 1: A child with neurodevelopmental problems related to valproate exposure in utero

A 16-year-old boy had poorly controlled epilepsy from the age of 2 years with moderate intellectual disability. He was the only child of non-consanguineous parents and with no family history of intellectual disability. His mother had been diagnosed with juvenile myoclonic epilepsy at the age of 13 years, but her seizures had been well controlled on medication (valproate 700 mg twice daily) with no convulsions, jerks, or absences for over 20 years. She held a driving license and ran her own business. The pregnancy had been uneventful, with no seizures, and during it she had taken folate 5 mg daily alongside the valproate.

The boy's motor, verbal, and intellectual developmental milestones had been severely delayed. He had been diagnosed with severe autism, intellectual disability, behavioral issues, and a heart murmur. He required 24-hour supervision and personal care and had been unable to attend mainstream schooling. He had no brothers or sisters and his parents had since separated. His mother had recently taken antidepressant medication and expressed overwhelming guilt about having taken valproate in pregnancy.

The neurodevelopmental results are more favorable for other ASMs, with carbamazepine, lamotrigine, levetiracetam, and topiramate having reported rates of neurodevelopmental delay closer to the background rate.[76,80] However, most studies of neurodevelopment following exposure to ASMs in pregnancy have been small or have assessed neurodevelopment only at a young age. There is no available information yet on the neurodevelopmental effect of the other ASMs.

Some studies have attempted to better define the individual risks for ASMs and adverse fetal/infant outcomes, such as the risks for recurrence and pharmacogenetic influences.[81,82] There do appear to be some individual susceptibilities to such outcomes, but results to date have not provided any insight. Clearly, there is still much to be learned.

In trying to reduce the risks of MCMs and neurodevelopmental delay, the ASM dose is important, although there is no safe dose for those ASMs associated with an increased risk of adverse fetal outcome. Valproate doses above 800 to 1,000 mg/day confer much higher risks, and EURAP showed that the MCM risk for those taking over 1,450 mg of valproate per day was around 25%, compared with 6.3% for women taking less than 650 mg/day.[50] Likewise, in the NEAD study, the mean full-scale IQ of those exposed to more than 1,000 mg per day of valproate was 94, compared with 104 for those taking less than 1,000 mg daily.[77]

Registry results for folate have not shown additional protection above background for pregnancies exposed to ASMs.[50,83] In contrast, some evidence suggests that preconceptual folic acid might protect against ASM-associated cognitive and neurodevelopmental delay. The NEAD study group reported on the impact of preconceptual folate on neuropsychological test performance, at ages 3 to 6 years, in children exposed to carbamazepine, phenytoin, lamotrigine, and valproate.[84] Benefits in folate use were seen with higher scores on the full-scale intelligence quotient (FSIQ), nonverbal and verbal tasks, and some executive function measures. Memory function and some other executive function measures were not affected by folate.

A prospective population-based study from the Norwegian Mother and Child Cohort study found the risk of autistic traits at the age of 18 months in children was lower with maternal periconceptual folic acid supplementation and with higher folate plasma concentrations at gestational weeks 17 to 19. The benefit of supplementation was not limited to those exposed to valproate.[85]

There is emerging evidence that folate taken during pregnancy may help fetal neurodevelopment and its use should be recommended.[84,85] However, there is no established optimal dose for the protective effects of folic acid. Various guidelines recommend doses, which range from 0.4 to 5 mg daily preconceptually and throughout the pregnancy.[44,86–88] However, it is often not used for various reasons, including socioeconomic status.[89,90]

Influence

The risks of MCM and cognitive and neurodevelopmental delay in pregnancies exposed to an ASM, and particularly to valproate, have prompted a change in prescribing and, in many countries, regulatory changes. In some jurisdictions, regulators have become increasingly proscriptive, requiring better provision of information for all women with epilepsy.[91] In the United Kingdom, for women taking valproate who are required to stay on it or who choose to stay on it, clinicians must consider the likelihood of them becoming pregnant, complete a recurring formal consent procedure annually at specialist review, and the patient must use highly effective contraceptive methods, such as intrauterine devices, depot medroxyprogesterone acetate, or sterilization.

There is guidance for those who opt to continue taking valproate, and for those who refuse to comply with the requirement to use highly effective contraception, and for those with intellectual disability where there may be difficulty enforcing the recommendations.[92] However, many women with epilepsy, especially those with a generalized epilepsy syndrome, clearly continue to rely on valproate as

an effective treatment. There is some indirect evidence that the priority to protect the development of the unborn fetus—women with epilepsy not being offered valproate or choosing to avoid it—may be exposing them to potentially modifiable risks, including the risk of sudden unexplained death in pregnancy (**Box 2**: **case history**). This is also the case with pregnancy,[93] where the risk of death is doubled during pregnancy and for the year after delivery.[94] It is undoubtedly challenging for women with epilepsy and their partners (as well as those caring for them) to balance these risks.

Box 2 Epilepsy-related death of a young woman who had never tried valproate

A 19-year-old woman was found dead in bed, alone in her student hall of residence. Her bedclothes were disrupted and there was blood around her mouth. She had taken ASMs since the age of 8 years. Typical seizures would occur in the morning, within an hour of waking, starting with a scream and then a 2-minute convulsion, during which she would stop breathing and become cyanotic. Levetiracetam had given reasonable epilepsy control in childhood, but 3 years earlier she had switched to lamotrigine monotherapy owing to mood change and irritability. She continued to have occasional generalized tonic-clonic seizures on awakening once or twice per year, especially after losing sleep or having drunk alcohol. She took an oral contraceptive and had no immediate pregnancy plans, but in previous discussions about valproate had expressed a preference to continue lamotrigine. Postmortem examination showed only a lateral tongue bite and pulmonary edema. The final diagnosis was of sudden unexpected death in epilepsy (SUDEP) relating to the epilepsy syndrome of generalized tonic-clonic seizures alone (formerly generalized tonic–clonic seizures on awakening).

Legacy

With greater knowledge and advice from regulatory authorities, there have been profound changes in the use of specific ASMs in women with epilepsy of childbearing age. This has occurred in all resource-rich countries where it has been studied, with reduced use of valproate and carbamazepine and increased use of lamotrigine and levetiracetam. These countries have seen a fall in MCM prevalence in children born to women with epilepsy, in the UK falling by 2.1% per year (1996–2016)[48] and in the EURAP study group by a total of 27% (2000–2013).[95] A study from tertiary epilepsy centers in the United States reported that only 5 of 402 women had used valproate during pregnancy.[96] In other countries, it remains difficult for women to switch to safer alternatives than valproate. For example, the Kerala Pregnancy Registry in India recently reported that 17.5% of all pregnancies were exposed to valproate monotherapy in the years spanning 2010 to 2019.[97]

The impact of avoiding less safe options in pregnancy on cognitive and other neurodevelopmental outcomes has yet to be confirmed, although the significantly negative impact of valproate on these outcomes suggests that this impact will be significant.

Future Directions

Ensuring ongoing improvements in the management of women with epilepsy during their childbearing years, aiming to improve outcomes for both mothers and their children, will likely remain among the most important aspects of epilepsy care. However, we need a concerted multidisciplinary, international approach to provide answers for most of the relevant questions. At present such information becomes available only slowly, and the process must be speeded up. It cannot be left only to interested researchers and clinicians to advocate for women with epilepsy and their unborn children: we need governments, regulators, and pharmaceutical companies to step up as well. Resource-rich nations, especially those with already well-developed methods for collecting the relevant information, should consider mandatory participation in pregnancy registries, with appropriate support and funding. There is still far too much delay from the introduction of any medication, including ASMs, to understanding its risks from exposure during pregnancy. For valproate, first licensed for clinical use in 1973, and despite its now recognized powerful teratogenicity, this delay was over four decades.

We need standardized studies of cognitive development and agreed widely adopted ways to undertake studies that can identify early signals of concern for ASMs in pregnancy. The gold standard will remain formal, blinded neuropsychometric assessment and measures of behavior to replicate study results. However, we urgently need studies focused on screening the early development of infants—for example, using the Ages and Stages Questionnaire administered by the mothers and fathers of children exposed to ASM in utero—with the potential greatly to accelerate the identification of teratogens. It would be useful to explore further ways to individualize a woman's risks—balancing the risk of deteriorating seizure control in pregnancy against the identifiable pharmacogenetic risks—and to explore how to minimize any risks. Thus, ASMs with known risks could be avoided, or continued only if there were no alternatives. We also need greater consideration of paternal concerns and paternal influences on risk.

Conclusion

Improving outcomes in pregnancy and reducing MCM risks must become a priority for all involved in the care of women with epilepsy. Effective preconceptual counseling, while not proven in randomized trials, would likely reduce MCMs rates. We must encourage early specialist referral of women at risk, and we need education and global advocacy to improve the situation worldwide for future generations.

Conflict of Interest
None declared.

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