

Management of epilepsy during pregnancy and lactation

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Abstract

Epilepsy is a group of neurological diseases characterized by susceptibility to recurrent seizures. Antiseizure medications (ASMs) are the mainstay of treatment, but many antiseizure medications with variable safety profiles have been approved for use. For women with epilepsy in their childbearing years, the safety profile is important for them and their unborn children, because treatment is often required to protect them from seizures during pregnancy and lactation. Since no large randomized controlled trials have investigated safety in this subgroup of people with epilepsy, pregnancy registries, cohort and case-control studies from population registries, and a few large prospective cohort studies have played an important role. Valproate, in monotherapy and polytherapy, has been associated with elevated risk of major congenital malformations and neurodevelopmental disorders in children born to mothers who took it. Topiramate and phenobarbital are also associated with elevated risks of congenital malformations and neurodevelopmental disorders, though the risks are lower than those of valproate. Lamotrigine and levetiracetam are relatively safe. Insufficient data exist to reach strong conclusions about the newest antiseizure medications such as eslicarbazepine, peramppanel, brivaracetam, cannabidiol, and cenobamate. Besides antiseizure medications, other treatments such as vagal nerve stimulation, responsive neurostimulation, and deep brain stimulation are likely safe. In general, breastfeeding does not appear to add any additional long term risks to the child. Creative ways of optimizing registry enrollment and data collection are needed to enhance patient safety.

Introduction

Women with epilepsy comprise almost half of the population with general epilepsy.¹ Many treatment decisions are not influenced by sex; however, the possibility of pregnancy and lactation are unique to women in their childbearing years. Antiseizure medications (ASMs) are often continued throughout pregnancy and lactation to mitigate the risks of seizures, making them critical times, owing to concerns for women with epilepsy, the fetus, and the child.

The early data on increased teratogenicity due to antiseizure medications raised enough concerns that several prospective pregnancy registries (table 1) were created to help decipher these risks with more accuracy.³⁻⁸ In the ensuing years, the development of new antiseizure medications has also been prolific (fig 1).⁹⁻¹⁰ Due to the nature of this field (randomizing women to placebo would be unethical), no randomized controlled trials have answered the questions of safety and teratogenicity. Therefore, prospective cohort studies, including registries,

provide the highest quality evidence from which to make treatment decisions. The large number of existing antiseizure medications makes it difficult to quickly collect appropriate sample sizes of exposures for individual drug treatments. Furthermore, the Food and Drug Administration implemented a new pregnancy labeling system in 2015, known as the pregnancy and lactation labeling rule (PLLR),¹¹ which replaced the former pregnancy risk categories (A, B, C, D, or X) with narrative based labeling requirements. The PLLR arguably deals with the overly simplistic nature of the former pregnancy risk categories, but it also puts the onus on healthcare professionals to analyze the risks and benefits of a drug for a specific patient. While aiming to provide more evidence based recommendations, the PLLR might have introduced some complexity that has affected uptake and general use.

This evidence based review will help clinicians as they encounter these difficulties while treating women with epilepsy. As we look to the future of treatment of other chronic diseases in women of

Table 1 | International prospective pregnancy registries for antiseizure medications

Registry	Date established	Description	No of enrollees	Website
The UK and Ireland Pregnancy Register	1996 for UK 2001 for Ireland	Prospective; national self-enrollment and physician enrollment	10 766 (as of 2016 per website)	http://www.epilepsyandpregnancy.co.uk/
North American Antiepileptic Drug Pregnancy Registry	1997	Prospective US and Canada; self-enrollment	13 500 (as of 2021 per website)	https://www.aedpregnancyregistry.org/
The European and International Registry of Antiepileptic Drugs in Pregnancy -EURAP	1999	Prospective >40 countries involved; physician enrollment	29 488 (as of April 2023)	https://eurapinternational.org/
Kerala Registry of Epilepsy and Pregnancy	1998	Prospective; single center; physician enrollment	Registry audit from a recent paper reported 1469 enrollees from 2010 to 2019 ²	None
The Australian Pregnancy Register of Antiepileptic Drugs	2000	Prospective; national; self-enrollment and physician enrollment	2516 (as of 2019 per website)	https://www.epilepsy.org.au/apr-registration/

childbearing age (HIV, depression, migraines), this review will inform and motivate data scientists, epidemiologists, and health policy makers to design more efficient data collection tools, analytics, and other creative study designs that will improve clinical care.

Epidemiology

About 50 million people have epilepsy globally.¹² Middle income and low income countries have a higher incidence of epilepsy (80% of active epilepsy cases) than high income countries.

In the United States, about three million adults have epilepsy.¹³ The prevalence in women and girls is 46.2 per 100 000, compared with 50.7 per 100 000 for men and boys.¹⁴ The number of women of childbearing age with epilepsy is estimated to be at least half a million,¹⁵ with about 24 000 giving birth annually.¹⁶ Fetal exposure to antiseizure medications occurs in about one out of every 50 pregnancies.¹⁷

Methods

Both authors searched PubMed and Medline-Ovid, limiting the dates from 1990 through September 2022. Searching for “epilepsy and pregnancy” identified >10 000 articles. This was limited by “clinical trials”, giving 546 articles, of which 31 were found to be directly relevant. Other search terms included “fertility” AND “women with epilepsy”, “first generation antiepileptic drugs” AND “teratogenicity”, “second generation antiepileptic drugs” AND “teratogenicity”, “third generation antiepileptic drugs” AND “teratogenicity”, “Depakote” AND “neurodevelopmental disorders”, “neurodevelopmental effects of antiepileptic drugs”, “lactation” AND “antiepileptic drugs”, “vagus nerve stimulation” AND “pregnancy”, “responsive neurostimulation” AND “pregnancy”, “deep brain stimulation” AND “pregnancy”, “neuromodulation” AND “pregnancy”. A list of pregnancy registries was compiled, and each registry website was reviewed. The Maternal Outcomes and Neurodevelopment Effects of Antiepileptic Drugs (MONEAD) website was also reviewed.¹⁸ Earlier review articles on these

subjects were examined to identify articles before 1990 for context and historical perspective. Included literature was restricted to randomized controlled trials, registry analyses, case-control studies from population level databases, cohort studies, and large hospital or single institution case series or case reports when the above were not available.

Pregnancy success and fertility in women with epilepsy

For women with epilepsy who want children, one of the first questions is if epilepsy or the use of antiseizure medications affects fertility. Results from the PubMed search showed 10 studies that investigated this question. One 1994 study, based on interviewing 1558 people with epilepsy and 316 siblings without epilepsy, showed that women with epilepsy were only 37% as likely to have been pregnant as their female siblings without epilepsy.¹⁹ Another study, based on the Northern Finland birth cohort, identified 222 people with epilepsy from a cohort of 12 058 patients with 39 years of follow-up, and showed that only people with active epilepsy in adulthood had fewer children; people who went into remission before adulthood had a similar number of children to those without epilepsy.²⁰ A Scandinavian birth registry study identified women with active epilepsy in the Kuopio University area of Finland, and showed that women with epilepsy had a similar number of children (2.1, standard deviation 1.3) to healthy women (2.1, standard deviation 1.2).²¹ More recently, retrospective analyses of registry data have shown reduced pregnancy rates and higher rates of assisted reproductive services in women with epilepsy, suggesting that women with epilepsy have more difficulty getting pregnant.^{22 23} It has also been noted that reduced fecundity trended higher in those on antiseizure medication polytherapy than those on no antiseizure medication,²³ but this trend could also be accounted for by more poorly controlled seizures that would necessitate antiseizure medication polytherapy. By contrast, one prospective cohort study, designed specifically to answer questions about pregnancy in women with epilepsy desiring pregnancy, showed that women

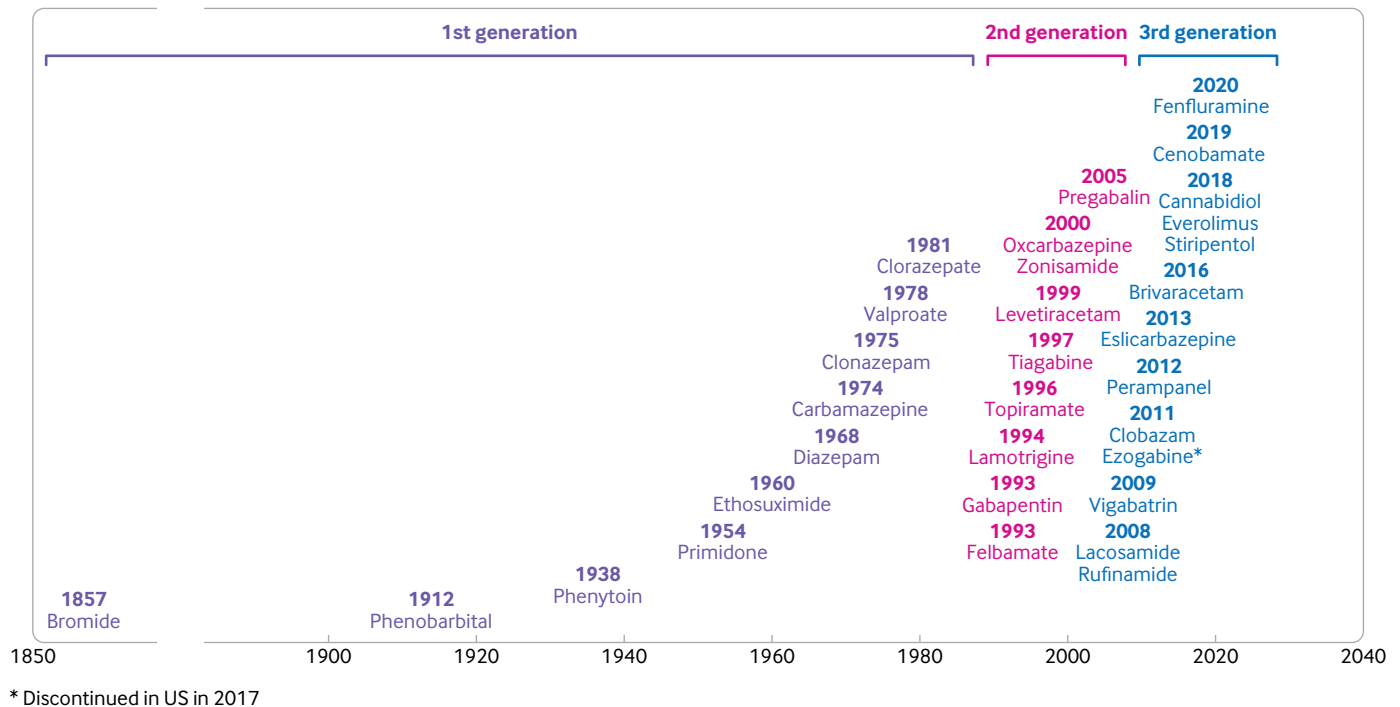


Fig 1 | Timeline of major antiseizure medication introductions in the US.

with epilepsy become pregnant at the same rate as other women.²⁴ To specifically isolate the effect of the epilepsy diagnosis, this study excluded women with a history of infertility, which might explain the difference compared with previous studies.

Few studies answer this question in lower income countries. One cross sectional study in Nairobi included 191 women with active epilepsy, and found that fertility rates were two-thirds lower than in the general population.²⁵ While socioeconomic factors, social stigma, and lower marriage rates could contribute to this finding, the use of first generation antiseizure medications could also influence the chances of successful pregnancy. In the Epilepsy Birth Control registry in the US, live birth-to-pregnancy ratios among sexually active women not using contraception were higher with the use of lamotrigine, a second generation antiseizure medication, compared with valproate, a first generation antiseizure medication.²³ However, further research is needed to investigate this possibility.

In summary, high quality evidence from a single prospective cohort study with controls shows that in the US, and probably other affluent countries, women with epilepsy have similar rates of successful pregnancies as women without epilepsy.

Pregnancy outcomes in women with epilepsy

How well do the pregnancies proceed, and how do babies do at birth beyond the question of teratogenicity? About 100 studies were found that dealt with pregnancy and perinatal outcomes. Data came from population based registries (eg,

Iceland) and pregnancy registries (eg, Finland), prospective cohort studies such as the Fertility and Birth Outcomes in Women with Epilepsy Seeking Pregnancy study and the MONEAD, and a few hospital based retrospective cohort analyses.

An Icelandic study analyzed population level data on 81 473 pregnancies between 1972 and 1990, and compared pregnancy outcomes in the 266 pregnancies in women with epilepsy.²⁶ Overall, similar rates of pregnancy related outcomes were observed, except that the rate of caesarean section was significantly higher in women with epilepsy compared with control patients (13% v 8.8%, $p=0.01$). A Finnish study analyzed data from 179 women with epilepsy compared with 24 778 controls, and found no difference in rates of caesarean section.²⁷ Most recently, an analysis of data from MONEAD also showed no difference in rates of caesarean section in women with epilepsy versus control patients.²⁸ Rates of caesarean section probably depend more on other factors such as local hospital culture than on patient variables; the highest rates of caesarean section are found in higher income countries.²⁹

In women with epilepsy, no difference in perinatal mortality or birth weight was found in the Icelandic study, but the rate of infants small for their gestational age was higher; infants of women with epilepsy also had smaller head circumference in the Finnish study. A similarly designed Danish study showed the risk of preterm birth increased as a function of the use of antiseizure medications.³⁰ A study from Norway suggested that the risk of low birth weight varies by drug.³¹ For example, topiramate exposure has an increased risk of microcephaly

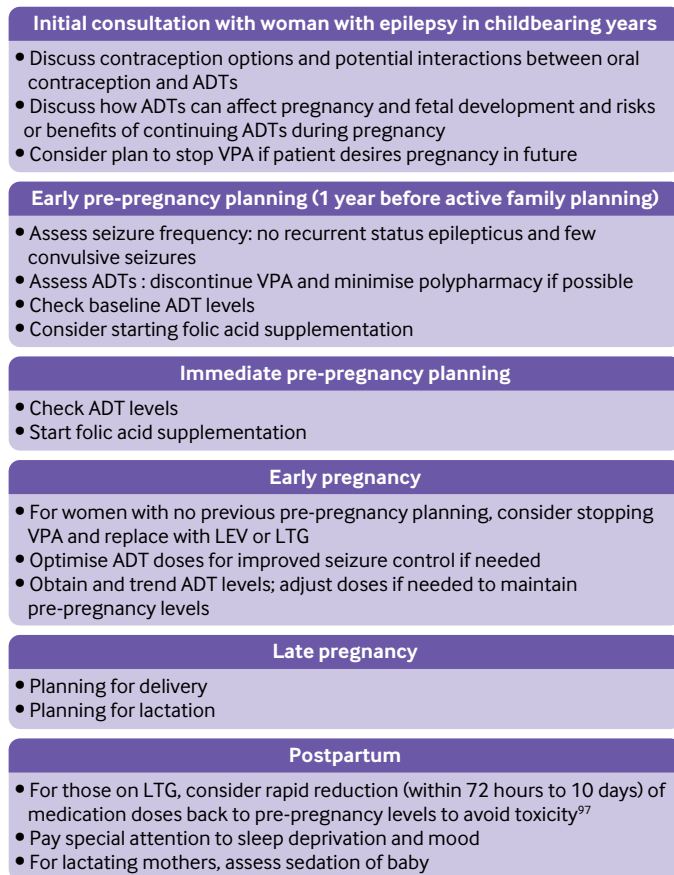


Fig 2 | Suggested treatment timeline for women with epilepsy planning pregnancy. ASM=antiseizure medication; VPA=valproate; LEV=levetiracetam; LTG=lamotrigine.

11.4% versus 2.4% (odds ratio 4.8, 95% confidence interval 2.5 to 9.3) and small for gestational age 24.4% versus 8.9% (3.1, 1.9 to 5.3). A review analyzed data from 38 studies published between 1990 and 2015 and showed small but significant increased risks of spontaneous miscarriage, antepartum hemorrhage, hypertensive disorders, induction of labor, caesarean section, preterm birth, and fetal growth restriction in women with epilepsy compared with controls.³² Notably, no difference was observed in fetal or neonatal mortality. Regarding mortality of children born to women with epilepsy, one Danish study analyzing data from 1981 to 2016 identified increased mortality in children born to women with epilepsy, but only in the years before 2000.³³ This suggests that other factors were likely responsible for that mortality, such as antenatal care or other health system effects, and not antiseizure medications. A later review analyzed 11 studies published between 2000 and 2016, and showed that epilepsy was associated with a small increased risk of fetal growth restriction (odds ratio 1.28, 95% confidence interval 1.09 to 1.50, $p < 0.05$), unaffected by antiseizure medications.³⁴ Another factor that seems to influence pregnancy outcomes is good antenatal care, including routine neurological care and pregnancy planning. One study based on a database prospectively collected between 2010 and

2018 in China compared pregnancy outcomes in unplanned and planned pregnancies in women with epilepsy, and showed that planned pregnancies had fewer induced abortions and preterm births.³⁵

Overall, evidence from cohort studies consistently shows that epilepsy and antiseizure medication are associated with an increased risk of fetal growth restriction, and pregnancy associated complications such as preterm births; however, clear evidence indicates that some antiseizure medications have a stronger influence on fetal growth, such as topiramate. Appropriate neurological routine care and pre-pregnancy planning can likely reduce those risks (fig 2).

Antiseizure medications and risks to the developing fetus and child

Congenital malformations

Major congenital malformations are structural abnormalities that carry medical, social, or cosmetic consequences requiring medical or surgical treatment.³⁶ In the US, major congenital malformations occur in about 3% of live births.³⁷ Major congenital malformations arise from genetic abnormalities or teratogenic exposures, or both. The data on major congenital malformations in women with epilepsy will be examined in this review.

Valproate was approved for use in 1978, and case reports in the 1980s showed that valproate preparations, and to a lesser extent phenytoin and phenobarbital, were associated with minor and major birth defects.³⁸⁻⁴⁰ However, these risks were not confirmed and compared among drugs until prospective pregnancy registries began enrolling pregnant patients in the 1990s. An important case-control study within the European Surveillance of Congenital Anomalies (EUROCAT) was published in 2010, and showed an increased risk of spina bifida, cleft palate, craniosynostosis, and polydactyly in children born to mothers who took valproate compared with those with no exposure to valproate preparations.⁴¹

Of the first generation antiseizure medications, valproate and its preparations have the highest risk of major congenital malformations, based on studies from all the major pregnancy registries;⁴²⁻⁴⁶ the strength of association was further confirmed by a later Cochrane review (table 2).⁴⁷ These data also support a dose-response effect, with higher risks seen at doses around 1500 mg daily and lower risks with daily doses < 800 mg.⁴⁶ The Tomson study, based on EURAP registry data, analyzed 7355 pregnancies between 1999 and 2016, and showed the prevalence of major congenital malformations in eight antiseizure medications (fig 3).⁴⁸ The first generation antiseizure medications phenobarbital and phenytoin had a prevalence of major congenital malformations of 6.5% (19 of 294 pregnancies) and 6.4% (8 of 125), respectively. The prevalence of major congenital malformations with carbamazepine was similar to phenobarbital and phenytoin at 5.5% (107 of 1957), and valproate had the highest prevalence

Table 2 | Overall major congenital malformation risk associated with antiseizure medication monotherapy

ASM	Compared with women without epilepsy	Compared with women with untreated epilepsy	Specific MCMs with statistically increased risk in subgroup analysis*
CBZ	RR: 2.01 (1.20 to 3.36) RD: 0.02 (0.00 to 0.03)	RR: 1.50 (1.03 to 2.19) RD: 0.01 (0.00 to 0.03)	Orofacial cleft/craniofacial malformations
GBP	RR: 0.61 (0.07 to 5.18) RD: -0.00 (-0.02 to 0.01)	RR: 1.16 (0.23 to 5.93) RD: -0.00 (-0.06 to 0.05)	None
LEV	RR: 2.16 (0.76 to 6.17) RD: 0.01 (-0.00 to 0.03)	RR: 0.32 (0.10 to 1.07) RD: -0.02 (-0.03 to -0.00)	None
LTG	RR: 1.68 (0.78 to 3.65) RD: 0.01 (-0.00 to 0.02)	RR: 1.07 (0.64 to 1.77) RD: 0.00 (-0.01 to 0.02)	None
OXC	RR: 1.94 (0.53 to 7.15) RD: 0.01 (-0.01 to 0.03)	RR: 2.75 (0.53 to 14.43) RD: 0.03 (-0.09 to 0.14)	None
PB	RR: 2.84 (1.57 to 5.13) RD: 0.04 (0.01 to 0.06)	RR: 1.95 (0.97 to 3.93), P=0.06 RD: 0.03 (-0.01 to 0.07)	None
PHT	RD: 2.38 (1.12 to 5.03) RD: 0.02 (-0.00 to 0.04)	RR: 2.40 (1.42 to 4.08) RD: 0.03 (0.01 to 0.06)	None
PRM	RR: 0.48 (0.03 to 8.43) RD: -0.04 (-0.12 to 0.03)	RR(FE): 2.81 (1.13 to 7.02) RR(RE): 3.92 (0.76 to 20.14), P=0.10 RD: 0.07 (-0.00 to 0.14)	None
TPM	RR: 3.69 (1.36 to 10.07) RD: 0.03 (0.01 to 0.05)	RR: 1.99 (0.65 to 6.08) RD: 0.02 (-0.02 to 0.05)	None
VPA	RR: 5.69 (3.33 to 9.73) RD: 0.08 (0.05 to 0.11)	RR: 3.13 (2.16 to 4.54), p<0.00001 RD: 0.06 (0.04 to 0.08)	Neural tube malformations, cardiac malformations, orofacial cleft/craniofacial malformations, skeletal/limb malformations
ZNS	RR: 0.44 (0.02 to 7.93) RD: -0.01 (-0.03 to 0.01)	RR: No studies RD: No studies	None

Data obtained from Weston J, Bromley R, Jackson CF, et al.⁴⁷

ASM=antiseizure medication; CBZ=carbamazepine; FE=fixed effect analysis; GBP=gabapentin; LEV=levetiracetam; LTG=lamotrigine; MCM=major congenital malformation; OXC=oxcarbazepine; PB=phenobarbital; PHT=phenytoin; PRM=primidone; RD=risk difference; RE=random effect analysis; RR=risk ratio; TPM=topiramate; VPA=valproate; ZNS=zonisamide.

*Subgroup analysis evaluated the following malformation categories: neural tube malformations, cardiac malformations, orofacial cleft/craniofacial malformations, skeletal/limb malformations; statistically significant results denoted in bold.

at 10.3% (142 of 1381). All registry analyses show the highest risk of major congenital malformation in children born to mothers who took valproate.⁴⁸⁻⁵⁴ The Cochrane review⁴⁷ examined 50 studies, with 31 studies included in a meta-analysis, with the following risk ratios when compared with children born to women without epilepsy:

- Phenobarbital n=345 versus 1591 (risk ratio 2.84, 95% confidence interval 1.57 to 5.13)
- Phenytoin n=477 versus 987 (2.38, 1.12 to 5.03)
- Carbamazepine n=1367 versus 2146 (2.01, 1.20 to 3.36)
- Valproate n=467 versus 1936 (5.69, 3.33 to 9.73)

This meta-analysis also included data on second generation antiseizure medications: zonisamide, lamotrigine, oxcarbazepine, gabapentin, topiramate, and levetiracetam. Of these, topiramate was the only one to show an increased risk of malformations: n=359 versus 442 (risk ratio 3.69, 95% confidence interval 1.36 to 10.07). This study showed a risk stratification with valproate having the highest risk, followed by modest increase with exposure to drugs such as topiramate and phenobarbital, and the lowest risk in drugs such as levetiracetam and lamotrigine. An examination of the North American Registry website registry data shows this stratification with current data (as of December 2022).⁵⁵

Based on these registry data, polytherapy with valproate clearly drives the risk, while data on polytherapy without valproate suggests that the

risks are lower.⁵⁶ The MONEAD study, a prospective observational study with controls, enrolled patients on polytherapy without valproate. The most common polytherapy combination of levetiracetam and lacosamide (43% of the polytherapy group) showed no increased risk of major congenital malformation, but the study might not have been adequately powered.⁵⁷ A Finnish study, comparing rates of major congenital malformation in women who continued antiseizure medication with those who discontinued antiseizure medication during pregnancy, also showed that polytherapy without valproate was not associated with increased risk of major congenital malformation.⁵⁸ In addition to the data on valproate, the Kerala registry showed duotherapy with topiramate had the highest risk of major congenital malformation (relative risk 14.62, 95% confidence interval 1.88 to 113.83).⁵⁹ Registry data from Australia and China show similarly elevated risks related to the use of topiramate, and also phenobarbital combinations.^{60 61}

Given the concerns about valproate risks to the fetus, attempts to wean valproate before or during pregnancy are common. However, caution is advised when considering this strategy, as it increases risk to women with epilepsy. An analysis of EURAP observational international registry of antiepileptic drugs and pregnancy data showed a twofold risk increase in generalized tonic clonic seizures among pregnant women who had valproate withdrawn or switched to another antiseizure medication during the first trimester of pregnancy.⁶² In a Norwegian

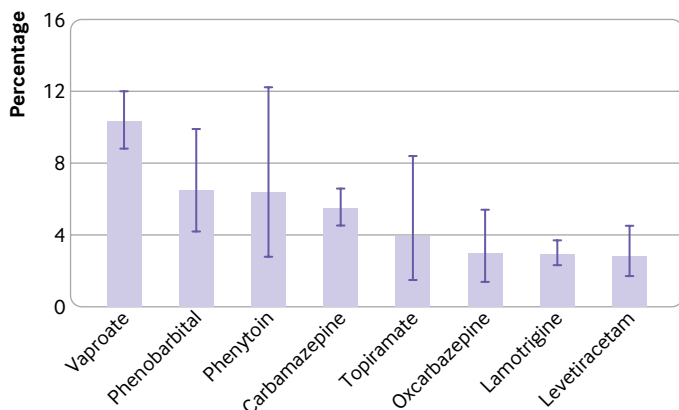


Fig 3 | Risk of major congenital malformations associated with perinatal antiseizure medication exposure. An analysis of data from the EURAP international registry examining prevalence of major congenital malformations in offspring with perinatal antiseizure medication exposure showed the prevalence to be 2.8% with levetiracetam, 2.9% with lamotrigine, 3.0% with oxcarbazepine, 3.9% with topiramate, 5.5% with carbamazepine, 6.4% with phenytoin, 6.5% with phenobarbital, and 10.3% with valproate. Data from Tomson T, Battino D, Bonizzi E, et al.⁴⁸

nested case-control study, lamotrigine, a commonly chosen antiseizure medication during pregnancy owing to its low risk of teratogenicity, was shown to have a higher risk of sudden unexpected death in epilepsy patients (SUDEP) compared with other antiseizure medications.⁶³ Fear of teratogenicity and lack of patient counseling can lead women with epilepsy to abruptly stop or reduce antiseizure medications without physician discussion. In one prospective cross sectional study, 66 of 365 women (18.1%) surveyed reported stopping or reducing antiseizure medications without input from their physician,⁶⁴ a choice that can lead to status epilepticus and increased risk of SUDEP. Management decisions should apply shared decision making between the woman with epilepsy and her physician, after a thorough discussion of risks and benefits of all available options from the perspective of the woman's safety, as well as that of the unborn child.

Overall, evidence from cohort studies/population and specific birth registry analyses consistently shows that exposure to valproate carries an elevated (2-3 times the baseline) risk of major congenital malformation. Lamotrigine and levetiracetam monotherapy have the lowest risk, and drugs such as topiramate and phenobarbital carry intermediate risk. Furthermore, polytherapy with valproate combinations, topiramate combinations, and phenobarbital combinations also carry elevated risk of major congenital malformation, but polytherapy without these drug treatments is not associated with an increased risk of major congenital malformation. No strong conclusions can yet be made on the risk of major congenital malformation with use of most of the third generation antiseizure medications. Management decisions need to balance patient choice and be made jointly between the woman with epilepsy and her physician.

Neurodevelopmental disorders

Case reports in the 1990s and early 2000s described lower intelligence and increased risk for developmental disorders, such as autism spectrum disorder, in children born to mothers who took valproate preparations,⁶⁵⁻⁶⁷ but the studies were small and often flawed. This propelled the launch of a large prospective cohort study in the US called the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD), which enrolled pregnant women between 1999 and 2004.⁶⁸ The NEAD study is an observational study that recently expanded to the MONEAD study, which has tracked not only the women, but the children born to mothers taking antiseizure medications. Analysis of children who were exposed to valproate, carbamazepine, lamotrigine, and phenytoin was performed at 3 years and 6 years of age. Cognitive outcome data from 309 children aged 3 were analyzed while controlling for maternal and other relevant characteristics, and valproate exposure was shown to be associated with lower IQ. This effect was also seen at age 6, with children who had valproate exposure having IQ scores 6-10 points lower than children exposed to lamotrigine, carbamazepine, or phenytoin.⁶⁹ Valproate seems to negatively impact verbal abilities more than non-verbal abilities. In a later analysis of data from the MONEAD cohort enrolled between 2012 and 2016, when most women took levetiracetam and lamotrigine, no significant difference in cognitive outcomes was observed in children aged 2 born to women with epilepsy, compared with controls.⁷⁰

A recent analysis of the Nordic register based study of antiepileptic drugs in pregnancy (SCAN-AED) has spurred increased caution in the prenatal use of topiramate, and triggered a safety review in the UK.⁷¹ This large observational cohort study assessed the cumulative incidence of autism spectrum disorder and intellectual disability at 8 years of age in those with prenatal exposure to 10 antiseizure medication monotherapies and five duotherapies. In this study, both topiramate and valproate were associated with a greater risk of autism spectrum disorder (4.3% and 2.7%, respectively) and intellectual disability (3.1% and 2.4%, respectively) in a dose dependent fashion, when compared with unexposed children (1.5% and 0.8%, respectively). Not surprisingly, the safest duotherapy in this study was the levetiracetam-lamotrigine combination. All other duotherapies showed an increase in neurodevelopmental disorders, though sample sizes were smaller than the monotherapy groups. The increased incidence of neurodevelopmental disorders in children exposed to topiramate prenatally contradicts previously reported findings from other observational studies.^{72 73} The common practice of stopping topiramate early in the prenatal course owing to concerns for major congenital malformations could have also attenuated results in previous studies.

In summary, persuasive data from prospective cohort studies, as well as analysis of registry data, indicate that valproate use during pregnancy is

associated with lower IQs and more developmental disorders in children with fetal valproate exposure. Topiramate might also be problematic, based on a cumulative incidence analysis from a population registry. Drug treatments like levetiracetam and lamotrigine have no such association.

Folic acid supplementation

Folic acid is essential for nucleic acid and DNA synthesis. Folic acid deficiency during pregnancy has been linked to increased risk of neural tube defects, as well as other major congenital malformations, and evidence supports the use of periconceptual folic acid supplementation to reduce these risks in the general population.⁷⁴⁻⁷⁶ For pregnant women with epilepsy, the question is whether they are at additional risk and whether higher doses of folic acid are needed.

Women with epilepsy have shown an increased risk of major congenital malformations; while this increased risk has been largely linked to specific antiseizure medications,⁴⁷ genetics could play a role in some cases. Multiple antiseizure medications have been shown to reduce serum folate levels.⁷⁷ One study also reported a low serum folate concentration in pregnant women with epilepsy as a significant independent risk factor for major congenital malformations (odds ratio 5.8, 95% confidence interval 1.3 to 27.0).⁷⁸ It follows that folic acid supplementation could benefit these patients. One analysis of Hungarian pregnancy registry data showed a reduction of major congenital malformations in children exposed specifically to carbamazepine, phenobarbital, phenytoin, or primidone in utero, when their mothers used periconceptual folic acid supplementation (1.27, 0.85 to 1.89), compared with those born to mothers who did not use supplementation (1.47, 1.13 to 1.90),⁷⁹ but this finding did not reach statistical significance. A UK study found that no children with major congenital malformations were born to women with epilepsy who took periconceptual folic acid.⁸⁰ Notably, the UK pregnancy registry, as well as those of other countries, lack conclusive data showing that folic acid supplementation reduces the risk of major congenital malformations in children born to women with epilepsy.⁴⁸ This suggests that the higher risk of major congenital malformations is caused by an alternate mechanism, cannot be overcome with folic acid supplementation, or the data to date lack the power to detect an effect modification.

Folic acid supplementation, however, has been shown to have neurocognitive benefits in children born to women with epilepsy. A study in Norway found an increased risk of autistic traits in children exposed to antiseizure medications perinatally when their mothers did not use periconceptual folic acid supplements compared with those born to women who did supplement with folic acid (minimum of 0.4 mg/day).⁸¹ This increased risk was noted in offspring at 18 months (adjusted odds ratio 5.9, 95% confidence interval, 2.2 to 15.8) and 36 months of

age (7.9, 2.5 to 24.9). Data from the NEAD study, a prospective, observational, multicenter study of 311 children born to women with epilepsy on antiseizure medication monotherapy, showed higher full scale IQ at 3 and 6 years of age in children born to women with epilepsy who took periconceptual folic acid supplements of at least 0.4 mg/day.⁸² No additional protection was seen in those who took higher dose folic acid supplements (>0.4-1 mg/day, >1-4 mg/day, and >4 mg/day). Other reported benefits of folic acid supplementation include decreased risk of spontaneous abortion and preterm birth.^{83 84}

Concerns have been raised regarding potential harms of high dose folic acid supplementation.^{85 86} A recent Scandinavian observational cohort study analyzing registry data of over three million mother-child pairs collected over 20 years found an increased risk of childhood cancer in children born to women with epilepsy prescribed periconceptual high dose (≥ 1 mg daily, mean dose 4.3 mg) folic acid supplements, compared with children born to women with epilepsy who were not prescribed high dose folic acid (adjusted hazard ratio 2.7, 95% confidence interval 1.2 to 6.3), with an absolute risk if exposed of 1.4% (95% confidence interval 0.5% to 3.6%), and an absolute risk if unexposed of 0.6% (0.3% to 1.1%).⁸⁷ This increased risk was not seen in children born to mothers without epilepsy who were also exposed to high dose folic acid (mean dose 2.9 mg), and it also could not be accounted for by any specific antiseizure medication exposure during pregnancy. One of the limitations of the study is the presumption that women who filled folic acid prescriptions took the drug treatment as prescribed and that those not prescribed high dose folic acid were not taking over-the-counter folic acid supplements. Dietary folate intake is also unaccounted for, and serum folate levels were not available for analysis. These factors should be considered in future studies on the topic.

In short, folic acid supplementation is advisable in pregnant women with epilepsy. Registry data for pregnant women with epilepsy has not yet shown a reduction of major congenital malformations with folic acid supplementation. However, strong evidence indicates neurocognitive benefits in children born to women with epilepsy who received periconceptual folic acid supplements of at least 0.4 mg/day. Further research is needed to establish optimal dosing recommendations, as well as to investigate the safety of high dose folic acid supplementation.

Vitamin K supplementation

The literature contains multiple case reports of hemorrhagic disease in neonates born to mothers taking enzyme inducing antiseizure medications.^{88 89} It has been hypothesized that enzyme inducing antiseizure medications cross the placenta and lead to an increased rate of oxidative degradation of vitamin K and resultant vitamin K deficiency in the fetus.⁹⁰ This led to a recommendation for pregnant women with epilepsy on enzyme inducing antiseizure medications to take an oral vitamin K supplement in

the final weeks of pregnancy.⁹¹ This recommendation was in addition to the standard 1 mg parenteral vitamin K supplementation given to all neonates at the time of birth. However, a large prospective study of >600 pregnant women with epilepsy taking enzyme inducing antiseizure medications (carbamazepine, phenytoin, phenobarbital, primidone, and oxcarbazepine) found no significant difference in the incidence of hemorrhagic disease of the newborn compared with the control group.⁹² Instead, the incidence of neonatal bleeding was increased when birth occurred before 32 weeks of gestation, or in the context of maternal alcohol abuse. No women in the study received antenatal vitamin K, and all neonates received parenteral vitamin K after birth.

Given these findings, evidence is insufficient to recommend antenatal maternal vitamin K supplementation for all pregnant women with epilepsy taking enzyme inducing antiseizure medications. This conclusion is in keeping with the current American Academy of Neurology guidelines on the topic.⁹³

Antiseizure medication monitoring during pregnancy

In general, antiseizure medication levels are not frequently measured in people with epilepsy when seizures are controlled and who are without clinical signs of toxicity. Given the pharmacokinetic changes that occur during pregnancy,⁹⁴ an argument can be made to monitor antiseizure medication serum levels closely in this context, as tonic clonic seizures during pregnancy can cause decreased fetal heart rate, maternal and fetal hypoxia and acidosis, and possibly contribute to miscarriage.⁹⁵ The logical follow-up question is whether changes in serum concentrations of antiseizure medications lead to a clinically significant impact on seizure frequency that would warrant monitoring of antiseizure medication levels. Two retrospective cohort studies and two prospective observational studies have shown an increased frequency of seizures in pregnant women when antiseizure medication concentrations decreased below 65% of preconception concentrations.⁹⁶⁻⁹⁹ The MONEAD study expands on these results in a large prospective cohort study (351 pregnant women and 109 controls) that included antiseizure medication serum monitoring for multiple antiseizure medications.¹⁰⁰ Those in the pregnancy group taking lamotrigine, levetiracetam, oxcarbazepine, lacosamide, and zonisamide showed significant decreases in serum antiseizure medication dose normalized concentrations, while significant changes were not seen in dose normalized concentrations of topiramate, unbound carbamazepine, and carbamazepine-10,11-epoxide. The previously reported increase in seizure frequency accompanying decreased antiseizure medication concentrations was not replicated in this study, but the antiseizure medication doses were also increased throughout the study based on antiseizure medication concentrations, which could account for this discrepancy.

It remains to be seen whether serial monitoring of serum antiseizure medication levels during pregnancy leads to better outcomes than clinical monitoring alone. In one double blind, randomized trial nested within a cohort study, conducted at 50 obstetric and epilepsy clinics in the UK, pregnant women with epilepsy taking lamotrigine, levetiracetam, carbamazepine, or phenytoin, who also had serum antiseizure medication levels $\leq 75\%$ of their baseline level, were randomized to either a group in which antiseizure medication dose adjustments were determined by clinical features alone (n=130) or a group in which antiseizure medication dose adjustments were determined by antiseizure medication serum level in addition to clinical features (n=127).¹⁰¹ The time to first seizure between these groups was not significantly different (hazard ratio 0.82, 95% confidence interval 0.55 to 1.2). This finding could have been influenced by the threshold serum antiseizure medication level used as a criterion for group randomization, or possibly by variabilities in practice patterns of the clinicians across the study sites.

Collectively, evidence indicates that antiseizure medication concentrations of lamotrigine, levetiracetam, oxcarbazepine, lacosamide, and zonisamide decrease during pregnancy, and an increase in seizure frequency is associated with a serum antiseizure medication concentration of $\leq 65\%$ compared with preconception concentrations for women taking lamotrigine and levetiracetam. This supports routine antiseizure medication level monitoring for pregnant women with epilepsy taking these drug treatments and appropriate dose adjustments. In situations where monitoring is not possible, consideration could be given to empiric dose adjustments based on the typical pharmacokinetics of the drug treatment during pregnancy or the use of carbamazepine, which did not have the same fluctuations in concentration in the unbound form or metabolite in the MONEAD study. While topiramate also did not show significant fluctuations in concentration, it should be avoided when possible, owing to increased risk of major congenital malformations and possibly neurodevelopmental consequences. Additional research is needed to determine optimal frequency of antiseizure medication level monitoring, and whether it leads to better outcomes at a practical level.

Lactation

The period when a woman with epilepsy is lactating is also unique, and historically, there has been a concern that the risks of exposure to antiseizure medications could be too high for the infant. The NEAD and MONEAD studies offer the highest quality evidence to date, and support the practice of lactation for most women.¹⁰²⁻¹⁰⁴

The NEAD study, a prospective multicenter observational study, provided data of cognitive outcomes of children who were breastfed by a

mother on antiseizure medication monotherapy with carbamazepine, lamotrigine, phenytoin, or valproate, with a median breastfeeding time of six months.¹⁰² Out of a sample size of 199 children born to women with epilepsy in the US and UK, 42% were breastfed, and were found to have no statistically significant difference in IQ at age three years when compared with the children in the sample who were not breastfed. The analysis on this sample was subsequently extended to six years of age (42.9% of 181 children in the breastfed group, with mean breastfeeding duration of 7.2 months), and still, no significant difference in IQ was observed between the breastfed group and the non-breastfed group.¹⁰³ Additional measures of verbal, non-verbal, memory, and executive function were performed and showed superior verbal abilities (adjusted verbal index four points higher (95% confidence interval 0-7, $P=0.03$)) in the breastfed group. Similarly, the prospective Norwegian Mother and Child Cohort Study showed no adverse outcomes in social skills, language, or behavior at three years of age in children breastfed by mothers taking antiseizure medications (monotherapy with carbamazepine, lamotrigine, valproate, or polytherapy) compared with the non-breastfed group.¹⁰⁵

Moreover, the MONEAD study showed that breastfed infants born to women with epilepsy typically have a much lower antiseizure medication serum concentration than their mothers.¹⁰⁴ Of the 138 breastfed infants of women with epilepsy in the study population, 49.3% had antiseizure medication concentrations below even the lower limit of quantification. The exception to this was lamotrigine, a finding that highlights the importance of decreasing the lamotrigine dose expeditiously in postpartum women who required dose increases during pregnancy. Notably, this study only included women with epilepsy on monotherapy with carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate, or zonisamide. The lower serum concentrations could provide one explanation for the lack of deleterious effects attributable to breastfeeding in children born to women with epilepsy. However, many antiseizure medications currently in use were not included in these studies.

Some experts have recommended breastfeeding with caution for women with epilepsy taking phenobarbital, primidone, clobazam, and clonazepam, with close monitoring of the infant for lethargy, hypotonia, poor suck, or apneas.¹⁰⁶ Breastfeeding for women with epilepsy taking felbamate is generally avoided owing to lack of safety evidence for the infant and known risks of acute hepatic failure and aplastic anemia in adults.^{107 108} Another notable feature of the NEAD and MONEAD studies is that antiseizure medication exposure in utero preceded exposure during breastfeeding. Future research including women who require the addition of new antiseizure medications post partum would also be valuable and allow for more objective

guidance in the treatment of postpartum women with new onset seizures, or those who require an antiseizure medication for another indication outside of epilepsy.

In general, women with epilepsy should be encouraged to breastfeed. The evidence suggests that breastfeeding is safe when the mother is taking carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate, zonisamide, or phenytoin. Close monitoring for the infant could be advisable when the breastfeeding mother is taking phenobarbital, primidone, clobazam, or clonazepam. Further research is needed for women with epilepsy using newer antiseizure medications, but breastfeeding could be considered in such cases with close infant monitoring following careful discussion between patient and physician.

Emerging treatments

Neuromodulation safety in pregnancy

Vagus nerve stimulation has been used as adjunctive treatment for intractable epilepsy since the 1990s. The largest study to date investigating the safety of vagus nerve stimulation for women with epilepsy and fetal outcomes during pregnancy was an international observational cohort study using primarily EURAP registry data, as well as Australian and UK pregnancy registries.¹⁰⁹ Twenty-six pregnancies were assessed in 25 women, with most women (70%) on antiseizure medication polytherapy. One major congenital malformation was reported (3.9%, 95% confidence interval 0.1% to 19.6%), in keeping with the major congenital malformation rate seen in women on antiseizure medication without vagus nerve stimulation. The authors also noted a higher proportion of women requiring obstetrical interventions (53.9%, 33.4% to 73.4%) compared with the EURAP average (48.2%, 47.2% to 49.1%). Although vagus nerve stimulation could in theory have led to physiological changes contributing to the need for obstetrical interventions, the higher number of obstetrical interventions might also be accounted for by the population of women who receive vagus nerve stimulation, those with intractable epilepsy. Over 90% of the women included in the study had seizures during pregnancy, which also could contribute to the need for obstetrical interventions. Overall, no evidence indicated teratogenicity from vagus nerve stimulation, and no clear causation for the increased obstetrical interventions was reported. Though most women receiving vagus nerve stimulation during pregnancy had the device implanted before conception, in one case report, a woman with intractable epilepsy safely underwent vagus nerve stimulation implantation and activation during the third trimester of pregnancy, resulting in improved seizure control.¹¹⁰

Responsive neurostimulation is another option for adjunctive treatment and has been FDA approved since 2014 for adults with intractable focal onset epilepsy with one to two foci. The largest study to date focusing on the maternal and fetal safety and

outcomes of women with epilepsy and responsive neurostimulation adjunctive treatment was a retrospective cohort study including data from nine US epilepsy centers between 2014 and 2020, that described outcomes of 10 patients and 14 pregnancies.¹¹¹ No major congenital malformations were reported, and the rate of obstetrical complications was in keeping with that expected for women with epilepsy.

In 2018, deep brain stimulation received FDA approval as an adjunctive treatment for people with intractable focal onset epilepsy. As the newest of the neuromodulatory treatment options in the US for epilepsy, the data on pregnant women, specifically for intractable epilepsy treatment, is sparse. One case report of two women with epilepsy with deep brain stimulation found no teratogenicity concerns or changes in the expected obstetrical complication rate.¹¹² Additional data are available for deep brain stimulation for other indications outside of intractable epilepsy. A case series of 11 women with deep brain stimulation for movement disorders or psychiatric indications also supported the safety of deep brain stimulation for both mother and baby.¹¹³

Overall, the neuromodulatory treatments for intractable epilepsy seem to be safe in pregnancy, though the sample sizes of the case series/case reports leading to this conclusion are small. Additional data for these devices are being gathered through the pregnancy registries, and updates are certain to follow, as the use of neuromodulatory devices becomes more commonplace in women with epilepsy. Should the safety continue to be shown in pregnant women with epilepsy, future consideration could be given to using these treatments to help reduce the number of antiseizure medications required in women with epilepsy who are on polytherapy and considering pregnancy.

The newest antiseizure medications and pregnancy

The use of antiseizure medications approved by the FDA over the past 10 years has become more frequent, but antiseizure medications such as eslicarbazepine, perampanel, brivaracetam, cannabidiol, and cenobamate are not yet included in the available pregnancy registry data.⁵⁵ Standard practice encourages the use of antiseizure medications known to be safe in pregnancy in women of childbearing age, which could contribute to the dearth of data on the newer antiseizure medications in pregnant women. Those who require these newer agents to control seizures should be encouraged to enroll in the pregnancy registries, to document outcomes and contribute to the available data in this area.

Registries face specific challenges; for example, not all women contribute their data. Consideration should be given to mandating data collection for all women who are on chronic drug treatment, like mandated data collection for hemoglobinopathies in all black women in the US. In the case of hemoglobinopathies, testing is completed by obstetricians; a case can be made to have hospitals

and obstetrics and pediatric clinics collect important variables without depending on the specialist neurologist. Data from middle income and lower income countries are also sorely needed. One example describes a multicountry, community based registry not limited to one disease.¹¹⁴ We hope that registries will be able to work more collaboratively to increase sample sizes.

In brief, the safety of most of the newest antiseizure medications is not yet known. We need to enroll a greater percentage of women with epilepsy in pregnancy registries, and for registries to collaborate internationally.

Guidelines

The International League Against Epilepsy (ILAE) recently surveyed its members to ascertain the use of guidelines on this topic, and concluded that guidelines in many countries were outdated and too vague regarding questions such as neurodevelopmental outcomes, antiseizure medication choice, drug monitoring during pregnancy, and breastfeeding.¹¹⁵ Many countries (35% of those who completed the survey), therefore, use guidelines from the American Academy of Neurology (AAN), American Epilepsy Society (AES), or the UK's National Institute for Health and Care Excellence (NICE).

Both the AAN and NICE have guidelines that pertain to women with epilepsy during pregnancy and postpartum periods. The AAN guidelines were originally published in 2009 and reaffirmed in 2013 and 2022, per the AAN website.^{93 116-118} They are evidence based and cover teratogenesis and perinatal outcomes, obstetrical complications, and change in seizure frequency and management during pregnancy including blood levels, folic acid supplementation, vitamin K, and breastfeeding. NICE guidelines are also evidence based,¹¹⁹ and its website includes links to an adverse event reporting system (the yellow card app).¹²⁰ Few studies seem to cover knowledge of these specific guidelines by treating obstetricians; however, the evidence based guidelines by the Royal College of Obstetricians and Gynaecologists for epilepsy in pregnancy offer guidance that is largely consistent with that given by the AAN.¹²¹ The biggest point of divergence between these guidelines seems to be a lack of a consistent dose recommendation for folic acid supplementation in women with epilepsy, with guidance ranging from 0.4 to 5.0 mg/day.^{93 121} This wide range is not surprising, given the dearth of high quality evidence regarding the optimal dosing of folic acid supplementation in this population as discussed previously in this review. A 1996 study suggested that obstetricians in Scotland could benefit from increased collaboration with neurologists when treating pregnant women with epilepsy.¹²²

Guidelines specific for middle and low income countries are needed, considering the dramatically different healthcare landscape. In 2011, the World Health Organization released evidence based epilepsy care guidelines to be used in low and

middle income countries.¹²³ With regard to women with epilepsy, these guidelines recommended the avoidance of valproate and polytherapy (compared with safer drugs carbamazepine, phenytoin, and phenobarbital) and recommended folic acid supplementation. This guideline has not been updated as of December 2022, but the access to second generation antiseizure medications such as levetiracetam or lamotrigine is probably limited or unreliable. In addition, even though epidemiologic research and registries are few and far between,¹²⁴ when they are attempted, facilities should collect data on all relevant diseases; for example, drug treatments used for HIV and exposure to antimalarials should be documented. It might be easier to feed these data into well known registries that exist already, such as through WHO, or perhaps even registries such as EURAP. Enrollment should not be dependent on high level experts who will not be available; criteria should be simplified to allow trained non-technical staff members to help with data collection.

Conclusion

Rates of successful pregnancy in women with epilepsy are generally comparable with other women, if they obtain prenatal care and avoid high risk drug treatments such as valproate and topiramate. Antiseizure medications have different risks of major congenital malformation, with valproate having the highest risk. Phenobarbital and topiramate are also problematic, although lower risk than valproate. Phenytoin and carbamazepine are even lower risk, and levetiracetam and lamotrigine have the lowest risks, approaching the risk levels of healthy controls. With regard to cognitive outcomes, fetal valproate exposure is associated with lower intelligence in children when compared with carbamazepine, phenytoin, and lamotrigine. Fetal valproate and topiramate exposure are associated with increased risk of developmental disorders such as autism spectrum disorder. The use of valproate (and potentially topiramate and phenobarbital) should be avoided in women of childbearing age, unless the prescriber and the patient have an explicit agreement.

Too few studies have been done on the best approach for antiseizure medication serum level monitoring during pregnancy, but it seems reasonable to check and adjust the levels of those drug treatments that are known to decrease significantly.

QUESTIONS TO HELP PROMOTE EQUITABLE CARE AROUND THE WORLD

- Can low income and middle income countries afford to consistently have safer drugs on their national formularies?
- How can low cost pregnancy surveillance systems be designed in low income countries to help gather data to inform health risks associated with chronic treatment in women of childbearing age (malaria, epilepsy, HIV, etc)?
- Can low income and middle income countries depend on the data collected from higher income countries to inform their national health policies?

Though many antiseizure medications are present in breast milk, lactation does not appear to confer any measurable long term risks for the child, and so should be encouraged.

Data on the newest antiseizure medications are limited, so they cannot be confidently recommended for pregnancy at this time.

Ongoing pregnancy registries have been important in this population and could be optimized by improved international collaborations and increased emphasis on enrollment.

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QUESTIONS FOR FUTURE RESEARCH

- Does animal data on teratogenicity correlate with safety in humans?
- What are the risks of antiseizure medication in people without epilepsy? (Many antiseizure medications are used for pain and psychiatric disorders.)
- How many exposures are needed to know whether a typical antiseizure medication is safe for pregnancy? Can predictive modeling and other big data principles be used to define simple timeframes for when a drug is deemed to be safe?
- How can more women be enrolled in pregnancy registries in the US, where enrollment is voluntary? Should neurologists be bypassed?

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