Management of reproductive risks in people with epilepsy

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Epilepsy is a common neurological condition worldwide, presenting unique management challenges for those affected during reproductive age. The effectiveness of contraceptives can be modified by antiseizure medication treatments and pregnancy can alter the pharmacokinetics of antiseizure medications. Furthermore, although treatment with some antiseizure medications convey lifelong risks to offspring, inadequately controlled epilepsy can lead to injury or, in rare cases, death of the mother. In this complex set of circumstances, safe and effective antiseizure medication treatment, evidence-based decision making regarding contraceptive selections, and clear counselling and risk minimisation are imperative. Although risk–benefit decision making has become standard clinical practice for the management of women with epilepsy of childbearing age, reproductive treatment considerations could also be relevant for men. Most young adults with epilepsy live in low-income and middle-income countries, where access to contraceptives, antiseizure medications with adequate safety profiles, and reproductive care and counselling can be scarce. Strategies to optimise care for people with epilepsy in all stages of their reproductive journey must be tailored for resource-limited settings to improve parent–child health worldwide.

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Introduction

Epilepsy is among the most common neurological disorders, with an estimated 50 million people living with the condition worldwide—80% of whom reside in low-income and middle-income countries (LMICs).[1] Globally, around 15% of women with epilepsy are of childbearing age.[2] Reproductive risks associated with epilepsy must elicit clinical considerations to ensure safe pregnancies for women with epilepsy and their children. For most women, antiseizure medications are essential to reduce the elevated risks of mortality and morbidity associated with uncontrolled seizures;[3] however, some of these medications confer increased risks for their offspring.[4] Access to antiseizure drugs with acceptable reproductive safety profiles, as well as preconception epilepsy counselling, is often scarce in LMICs. Thus, strategies for improving reproductive outcomes for people with epilepsy must be tailored to management in resource-limited settings.

Although risk–benefit decision making has become standard practice for women of childbearing potential with epilepsy, recent research and updates to regulatory guidance highlight the growing relevance of treatment considerations for men of reproductive age.[5] Other advances have raised questions about the optimal dose of folic acid that should be used for women with epilepsy of childbearing potential,[6] documented the challenge of managing antiseizure medication levels during pregnancy,[7] and identified potential teratogenic risks beyond those known for valproate.[1,4] In this Review, we will examine the new evidence shaping the clinical management of people with epilepsy of reproductive age.

We acknowledge that people identify themselves in diverse ways and that gender identity may not always align with terms used in clinical research. In this Review, we use the original study terms when citing previous work to maintain consistency with the original sources. However, more generally, we use the term people with epilepsy, recognising gender diversity.

Management for people of reproductive age

Around half of all pregnancies are unintended, with the proportion even higher in women with epilepsy of childbearing potential than in the general population[8,9] due to contraceptive failure associated with enzyme-inducing antiseizure medications, reduced adherence to contraceptive measures, and, in some settings, minimal access to family planning services.[4,8,9] The treatment of epilepsy for people of reproductive age has been less complicated for males, but recent investigations into valproate have led to the requirement of reproductive counselling in certain regions. Treatment of women and men with epilepsy of reproductive age should be optimised for both seizure control and potential pregnancy at the earliest possible opportunity, as stopping antiseizure medications can lead to breakthrough seizures, and certain mediciations carry increased risks to offspring.[10]

Person-centred[11] reproductive counselling in people with epilepsy should start before any chance of pregnancy and be regularly repeated (panel 1). Information is needed to guide counselling and antiseizure medication selection, including data on fetal survival, growth, and congenital anomalies, as well as outcomes only observable as the child ages, such as child health and neurodevelopmental outcomes.[2,4,12]

In this section, we will discuss the risks associated with antiseizure medication use during pregnancy on fetal and neonatal outcomes, as well as neurodevelopmental outcomes. We will then examine treatment consideration for men with epilepsy of reproductive age, before discussing decisions around antiseizure medication use and family planning for men and women with epilepsy of reproductive age.

Fetal and neonatal risks

Knowledge of fetal risks associated with antiseizure medication is frustratingly scarce. Currently, it takes decades to delineate high-risk antiseizure medications and, equally important, to confidently identify low-risk

Panel 1: **Reproductive counselling for people with epilepsy**

Access to counselling
All individuals with epilepsy of reproductive age should have access to comprehensive reproductive counselling.[1,2,4]

Counselling content
Counselling should focus on optimising antiseizure medication treatment, contraception, risk mitigation of sudden unexpected death in epilepsy, mental health, and safe childcare. Many patients also seek information about epilepsy heritability.

Risk reduction strategies
To minimise risks for both parents and infants, antiseizure medication with the highest evidence-based safety and efficacy should be prescribed at the lowest effective dose before attempting conception.[4]

Specific guidance for people with epilepsy of childbearing potential
Individuals should aim to reach stable seizure control for 9–12 months before pregnancy and receive guidance on antiseizure medication management throughout pregnancy, folic acid supplementation, pregnancy precautions, obstetric and neurological care, and breastfeeding practices.

Shared decision approach
Counselling should be person-centred, respecting individual preferences and values, and use shared decision-making models such as the Three-Talk Model[11] (figure 1) to support informed decision-making and improve treatment quality.

Effective risk communication
Risk discussions should use absolute numbers rather than relative risks or percentages. For example, stating: among 100 children born to fathers using valproate, five to six were diagnosed with a neurodevelopmental disorder, compared with two to three of 100 children born to fathers using levetiracetam or lamotrigine, provides better clarity than stating: the risk was 50% higher for children of fathers using valproate.

Research and development needs
Further work is needed to optimise preconception counselling in low-income and middle-income countries and to understand preconception counselling needs for people with epilepsy who produce sperm. Developing culturally and linguistically appropriate physical or digital resources, such as information leaflets, videos, or option grids, is essential to support shared decision-making across diverse health-care settings.[11]

antiseizure medications, undermining evidence-based care. Risks of poor outcomes in offspring vary by antiseizure medication type, dose, and gestation period of exposure.[12]

Valproate use in women with epilepsy of childbearing potential is now under regulatory restriction in several regions worldwide due to its high teratogenic properties across several fetal and longer term outcomes. The most recent estimates place the risk of major congenital anomalies at around 9%,[13] with the absolute risk differences in comparison to other antiseizure medications ranging from 5% to 8%.[13] However, the risk is up to 25% with doses of more than 1450 mg/day.[14] Carbamazepine, phenytoin, phenobarbital, and topiramate are also associated with increased risk of major congenital anomalies, although a lower risk than valproate exposure (figure 2).[4,13,15] Current data suggest that second and third generation antiseizure medications (introduced after 1990) have lower rates of risk of congenital anomalies, except for topiramate that has a risk of around 4%.[4,13] Lamotrigine and levetiracetam appear to be associated with the lowest level of risk (figure 2), but not every study has been consistent on this finding.[16] Despite the variance in statistical significance across some studies, likely arising from different methodological approaches, different data sources show similar absolute risks for the commonly used antiseizure medications.[4,13,14,16]

Investigations have shown that clinicians should be vigilant for not only congenital anomalies. Newer antiseizure medications, such as topiramate[17–19] and potentially oxcarbazepine,[18] carbamazepine,[18] clonazepam,[18] and zonisamide,[17] have been associated with an increased risk of fetal growth disruption (figure 2), with higher rates of babies born small for gestational age than in general population. Many other newer antiseizure medications remain without data.

Neurodevelopmental risks

Children exposed to valproate in utero more often have poorer functional outcomes, including in cognitive, social, and behavioural skills,[20,21] leading to higher rates of autism spectrum disorder, intellectual disability, and attention-deficit hyperactivity disorder both in comparison with the general population and children exposed to other antiseizure medications.[22–24] The symptoms of in-utero valproate exposure co-occur in a recognisable clinical presentation,[29] including major and minor congenital anomalies, facial dysmorphism, somatic health issues, and neurodevelopmental disorders known as fetal valproate spectrum disorder (ICD-11 LD2F.03).[29] The exact number of people affected worldwide, and the outcomes in adulthood, remain unknown. Preclinical studies have suggested that some parts of the valproate-associated phenotype might be transferred through up to three additional generations[30] via epigenetic mechanisms. Evidence of this phenomena in human lineages is rare,[31] but highly concerning and requires investigation.

Recent findings indicate that neurodevelopmental disruption should also be considered for antiseizure medications other than valporate. Following evidence from the SCAN AED collaboration (a population-based cohort study using health registry and social registry data from Denmark, Finland, Iceland, Norway, and Sweden),[22] some regions, including the EU and UK, introduced a pregnancy prevention plan for topiramate[32,33] due to its association with high risks of some major congenital anomalies,[4,13] adverse fetal growth outcomes,[17–19] and potential neurodevelopmental effects.[22] However, the extent and nature of neurodevelopmental risks associated with topiramate remain uncertain. The SCAN AED collaboration found a dose-dependent risk for autism spectrum disorder and intellectual disability, with adjusted hazard ratios (HRs)

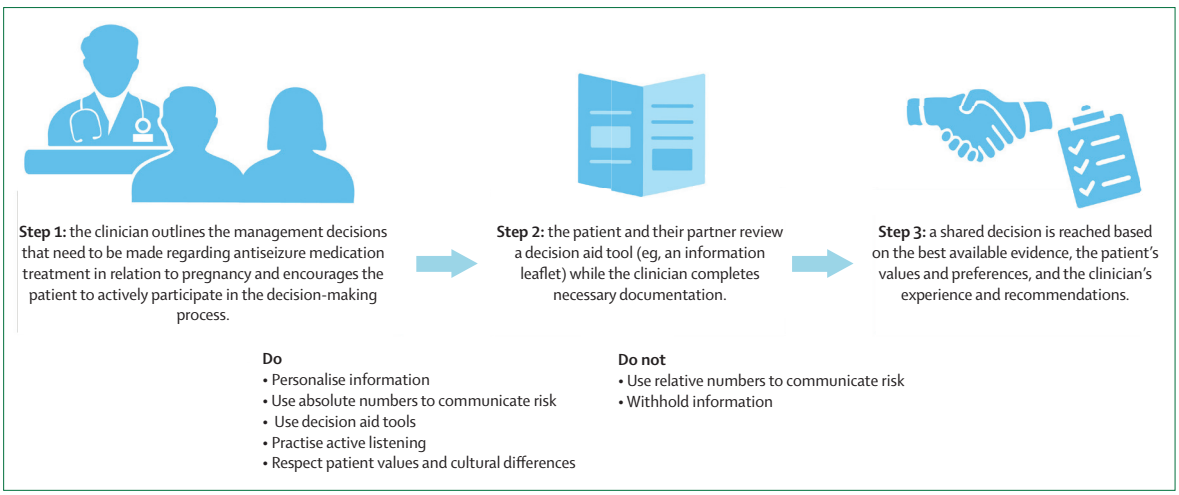

Figure 1: **The Three-Talk Model: a shared decision-making framework**
The figure illustrates the Three-Talk Model, a shared decision-making framework comprising three steps. Step 1: choice talk; the clinician introduces the management options for a person with epilepsy planning pregnancy (eg, continuing, discontinuing, or switching antiseizure medications) and encourages active patient involvement. Step 2: option talk; the individual independently reviews decision-support tools, such as leaflets, option grids, or videos, to facilitate informed choice. If possible, this step can be done with a partner, caregiver, or nurse, while the clinician attends to other tasks. Step 3: decision talk; the clinician and the person with epilepsy jointly make a decision, integrating the individual's preferences and the clinician's expertise.

of 2·8 (95% CI 1·4–5·7) for autism spectrum disorder and 3·5 (95% CI 1·4–8·6) for intellectual disability,[22] along with increased rates of attention-deficit hyperactivity disorder compared with children of people with epilepsy who were untreated during pregnancy.[23] Although the study population included more than 20 000 pregnant individuals with epilepsy, fewer than 250 fetuses were exposed to topiramate, and only ten of these offspring were later diagnosed with neurodevelopmental disorders, resulting in imprecise risk estimates. Conversely, a US registry study with larger groups did not replicate the risk of autism spectrum disorder after covariate adjustment, although the postnatal follow-up was only 2 years.[17] A third study combining average data from medical records taken from the UK and Sweden (a total of 17 495 antiseizure medication-exposed participants) replicated the finding of an increased risk of intellectual disability but not for autism spectrum disorder, however when peformed only in mothers with epilepsy a higher autism spectrum disorder risk was observed.[34] The authors suggest that this finding reflects confounding by indication;[34] however, the potential impact of prolonged adherence to topiramate treatment for epilepsy, and the use of higher doses of topiramate should also be considered as an alternative reason for this association. Despite inconsistencies in neurodevelopmental findings between studies, the consistent evidence of increased risks of major congenital anomaly and fetal growth restriction underscores the need for cautious use of topiramate in women of childbearing potential. Although regulatory restrictions for topiramate aim to mitigate risks, clear counselling is also required for carbamazepine, phenytoin, or phenobarbital, which also pose increased risks[4,13] and moderate neurodevelopmental effects.[15,21,25]

Lamotrigine and levetiracetam are considered lower risk than valproate, topiramate, and carbamazepine based on current data for neurodevelopmental outcomes,[4,20,26,35] consistent with their risk profiles for congenital anomalies. Autism spectrum disorder, attention-deficit hyperactivity disorder, and intellectual disability are not more prevalent than in the general population in the offspring of those using lamotrigine and levetiracetam.[22,24,34] Lamotrigine has been extensively studied for its impact on cognitive function, but data on levetiracetam remain minimal. The MONEAD prospective, non-randomised study showed a novel association between higher third trimester serum levetiracetam concentrations and adverse neuropsychological scores in children at age 6 years,[35] underscoring the need for more data on the higher doses of the antiseizure medications that are considered safest.

Many antiseizure medications have little adequate data for use in monotherapy, with even more scarce evidence for dual or polytherapies.

Treatment considerations for men with epilepsy

Until recently, reproductive risks were primarily attributed to placental transfer of antiseizure medications. Although there was evidence of subfertility due to toxic effects of valproate on sperm,[36] poor fetal and child outcomes had not been linked with paternal valproate use. However, reports of adverse outcomes in children of fathers and grandparents exposed to valproate, and rodent models showing valproate-induced epigenetic sperm changes that are transferable to subsequent

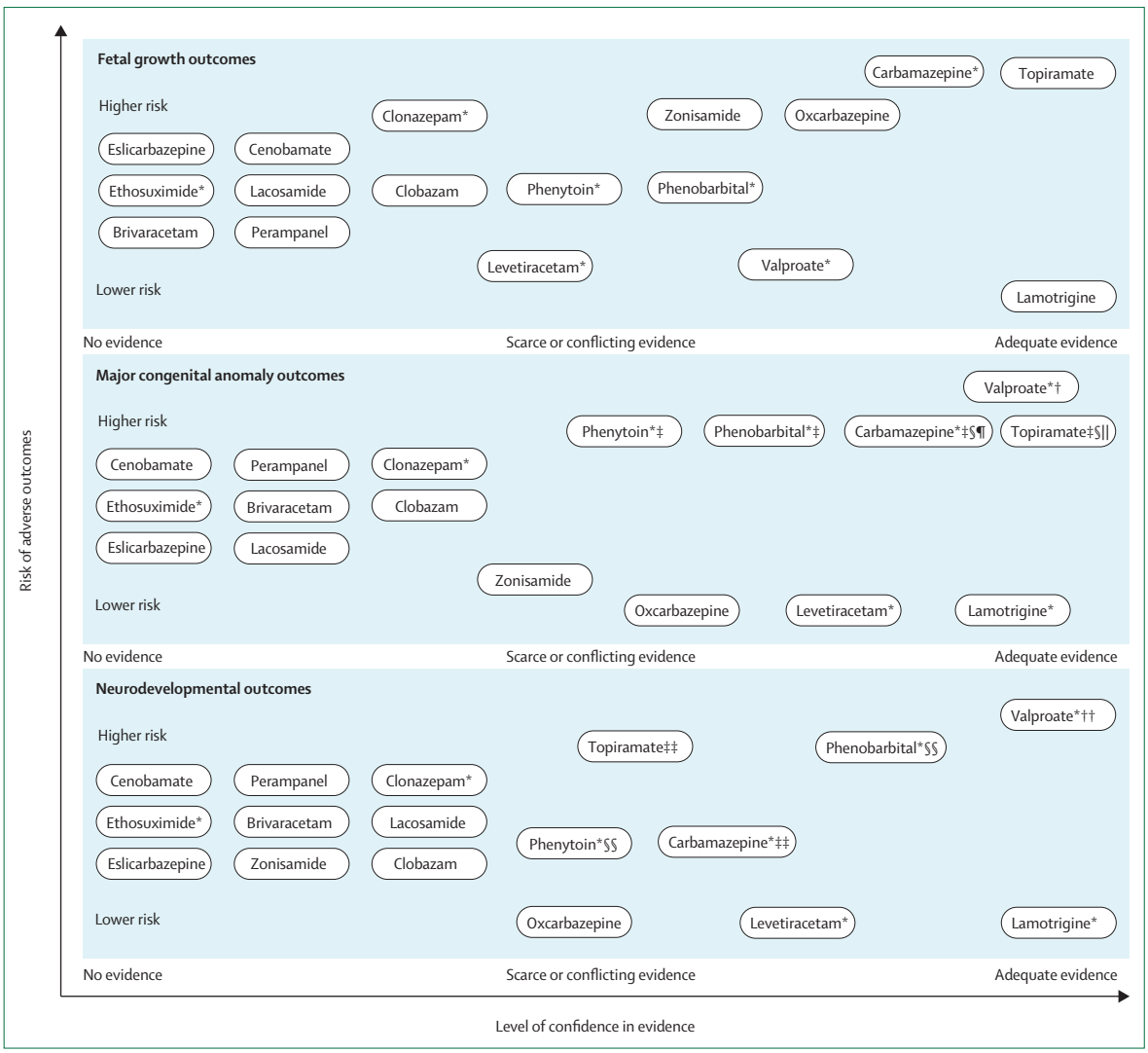

Figure 2: **Antiseizure medication risk across fetal growth, major congenital anomaly, and neurodevelopmental outcomes**
Information derived from multiple sources.[4,5,13-27] Medications with no or extremely scarce data are shown as moderate risk, due to the unknown association. *Included in the WHO Essential List of Medicines.[28] †Skeletal, limb, cardiac, and other anomalies. ‡Cardiac anomaly. §Skeletal anomaly. ¶Gastrointestinal. ||Orofacial. ††Autism spectrum disorder, cognitive, and attention-deficit hyperactivity disorder. ‡‡Autism spectrum disorder and cognitive. §§Cognitive.

generations,[30] prompted further investigations by market authorisation holders.[37]

The European Medicines Agency-mandated post-authorisation safety study used health records data from Denmark, Norway, and Sweden[38] and identified heightened neurodevelopmental risks with paternal monotherapy valproate use during spermatogenesis, compared with lamotrigine or levetiracetam. The pooled adjusted HR was 1·50 (95% CI 1·09–2·07), although it varied by country (table 1). Neurodevelopmental effects occurred in 5% of children whose fathers used valproate versus 3% of children whose fathers used lamotrigine or levetiracetam.[5,38] However, independent Danish analyses were unable to replicate the Danish risk estimates in the post-authorisation safety study (1·10, 0·88–1·37; table 1).[39] An earlier Swedish study had compared children of fathers not treated with antiseizure medications with children of fathers treated with valproate, reporting relative risks as 1·4 (95% CI 0·6–3·1) for autism spectrum disorder, 1·6 (95% CI 0·5–5·1) for intellectual disability, and 1·4 (95% CI 0·7–2·8) for attention-deficit hyperactivity disorder.[40] However, the study concluded that neurodevelopmental disorders in the children of fathers treated with valproate were likely attributable to epilepsy-related factors.

Regarding major congenital anomalies, the post-authorisation safety study reported a pooled unadjusted risk estimate of 0·8 (95% CI 0·49–1·29) for valproate, compared with levetiracetam or lamotrigine, in Denmark and Norway; although this finding was not statistically significant, heterogeneity between the two countries was observed.[38] Additional analyses from Denmark and

Sweden found no increased major congenital anomaly risks with paternal valproate use.[18,40] Despite unclear neurodevelopmental risks and no evidence of risk of congenital anomalies in humans, regulatory guidelines in some regions, including the EU and the UK, now recommend that men using valproate should not donate sperm and effective contraception should be used by their sexual partners, as well as maintaining these precautions for 3 months after discontinuation.[5] The UK's medicines authorities extended recommendations to require two specialists to confirm that alternative treatments are unsuitable for men younger than 55 years starting valproate,[41] generating substantial debate, and remains under review (with a recent reduction in requirements for men already taking valproate).[42–45] Although counselling is essential in cases when harm is likely, the benefits of stringent restrictions and the risks for men with epilepsy who need valproate treatment remain uncertain.

The strengths and limitations of current knowledge are covered in more detail in a review dedicated to this topic.[44] However, the discrepant and imprecise risk estimates also highlight the need for studies with diverse methodologies, including improved accuracy of outcome measurements, adequately powered studies, data from other geographical regions, and analyses accounting for genetic risk of neurodevelopmental disorders, as well as greater transparency in analytical methods.

For other antiseizure medications, no associated paternal risks are known, although this likely reflects data gaps rather than confirmation of safety. Danish studies have found an increased risk of congenital anomalies with paternal lamotrigine use, with one study reporting an odds ratio of 1·4 (95% CI 1·1–1·7) compared with unexposed fathers.[46] However, the interpretations of these findings are uncertain.

	Comparison	HR (95% CI)
Composite of neurodevelopmental diagnoses		
PAS Study (2023)[37,38]		
Denmark	Valproate *vs* levetiracetam and lamotrigine	1·34 (0·79–2·25)
Sweden	Valproate *vs* levetiracetam and lamotrigine	1·54 (0·95–2·51
Norway	Valproate *vs* levetiracetam and lamotrigine	1·52 (0·93– 2·49)
All studied countries	Valproate *vs* levetiracetam and lamotrigine	1·76 (0·83–3·71)*
Christensen et al (2024)[39]		
Denmark	Valproate *vs* general population comparator	1·10 (0·88–1·37)
Autistic spectrum disorder diagnoses		
Tomson et al (2020)[40]		
Sweden	Valproate *vs* general population control	1·4 (0·6–3·1)
PAS Study (2023)[37,38]		
Denmark	Valproate *vs* levetiracetam and lamotrigine	0·76 (0·30–1·89)
Sweden	Valproate *vs* levetiracetam and lamotrigine	2·68 (1·17–6·12)
Norway	Valproate *vs* levetiracetam and lamotrigine	Not reported
All studied countries	Valproate *vs* levetiracetam and lamotrigine	1·52 (0·83–2·81)*
Christensen et al (2024)[39]		
Denmark	Valproate *vs* general population comparator	0·92 (0·65–1·30)
Intellectual disability diagnoses		
Tomson et al (2020)[40]		
Sweden	Valproate *vs* general population control	1·6 (0·5–5·1)
Attention deficit hyperactivity diagnoses		
Tomson et al (2020)[40]		
Sweden	Valproate *vs* general population control	1·4 (0·7–2·8)

HR=hazard ratio. *Pooled HR.

Table 1: **Findings from population-based studies regarding use of valproate by men during spermatogenesis and offspring neurodevelopmental outcomes**

Decisions around continuing antiseizure medications

Following evaluation of an individual's epilepsy history, factors that could justify the continuation of an antiseizure medication with an uncertain or high-risk profile include epilepsy severity, outcomes of previous medication trials, and the potential for harm from seizures. A severe epilepsy history can include frequent generalised tonic–clonic seizures, previous status epilepticus, or nocturnal seizures. In women with epilepsy, these factors are associated with risks to the fetus and to the pregnant person.[2,4] Conversely, for other individuals with less severe or infrequent seizures, switching to a safer antiseizure medication, reducing the dose, or even discontinuing treatment might be appropriate. Infrequent focal aware seizures or absence seizures are less harmful, although some studies in women have found associations with personal injury, intrauterine growth restriction, and premature delivery.[2] For people with epilepsy in remission (based on clinical judgement), discontinuation should be considered.[2] Factors that increase the risk of recurrence following discontinuation include epileptiform abnormalities on EEG, duration of seizure freedom, number and duration of previous seizures, known focal pathology, and a history of febrile seizures.[47]

Given the potentially life-altering impact of antiseizure medication selection during reproductive age, the minimal evidence for many antiseizure medication exposures, and the modern emphasis on patient participation in decision making, joint decision making should be pursued whenever possible (figure 1).

Contraception

Family planning counselling is a crucial component of care for women with epilepsy of childbearing potential,[48] yet they still generally have lower rates of contraception use, in both high-income countries and LMICs.[48–50] Up to 30% of women with epilepsy of childbearing potential do not use highly effective birth control methods, and 7% potentially use hormonal contraception together with enzyme-inducing antiseizure medications, risking contraceptive failure.[8,48] Birth control advice should be provided before sexual activity begins and reviewed regularly,[51] particularly for those who take higher risk antiseizure medications.[2,4,8]

Antiseizure medication and contraception interactions

Interactions between combined hormonal contraceptives and potent CYP3A enzyme-inducer antiseizure medications, such as phenytoin, phenobarbital, and carbamazepine, accelerate the hepatic metabolism of the oestrogenic and progestogenic components of hormonal contraceptives, reducing contraceptive efficacy and potentially causing failure (appendix pp 1–2, table 1).[48,52–54] However, large discrepancies in hormonal interaction reports are common with newer antiseizure medications, such as cenobamate, topiramate, oxcarbazepine, eslicarbazepine acetate, and felbamate, that are low potency enzyme-inducing antiseizure medications and can cause selective reduction of progestin or estradiol concentrations in a dose-dependent manner.[52,55–58] For example, oxcarbazepine induces the metabolism of oral contraceptives for doses as low as 900 mg/day[59] and topiramate reduces ethinyl estradiol concentrations in a dose-dependent manner; 50–200 mg/day results in an 11–12% reduction, whereas 400 mg/day results in a 22% reduction.[59]

See Online for appendix

Antiseizure medications that do not induce CYP3A, such as lacosamide, levetiracetam, and zonisamide, are not expected to affect hormonal contraceptives substantially, whereas the interaction between lamotrigine and combined oral contraceptives is intricate. Some data show that lamotrigine accelerates progestin clearance, reducing progestin concentrations by about 20%, which heightens the risk of contraceptive failure with progestin-only oral contraceptives.[60] Conversely, combined oral contraceptives reduce lamotrigine concentrations.[48] This interaction is believed to stem from the oestrogen in combined oral contraceptives, which induces uridine-diphosphate glucuronosyltransferase enzymes, thereby increasing lamotrigine glucuronidation and excretion, leading to a 40–60% reduction in lamotrigine concentrations and potentially causing breakthrough seizures.[48,61] This reduction by oral contraceptives seems to follow a cyclic pattern, with the reduction occurring during the 21-day pill exposure period and a striking rise during the 7-day pill-free period.[60] However, data since 2020 also show that specific types of progestin can also reduce lamotrigine concentrations.[61,62] Furthermore, combined oral contraceptives containing drospirenone or levonorgestrel reduced lamotrigine concentrations, whereas those with gestodene did not. Further research is needed to elucidate the potential bilateral interactions between progesterone and lamotrigine.[48] The effects of non-oral hormonal contraception on lamotrigine pharmacokinetics are not well documented. Similar to oral hormonal contraceptives, withdrawing non-oral hormonal contraceptives, such as oestrogen patches and vaginal rings, during the medication-free week could lead to substantial fluctuations in lamotrigine concentrations.[48]

For other antiseizure medications, such as valproate and eslicarbazepine, uridine-diphosphate glucuronosyltransferase glucuronidation is also crucial for the metabolism with combined hormonal contraceptives; for example, valproate concentrations can be reduced by 20–40%.[63] Knowledge surrounding the interaction between hormonal contraceptives and newer antiseizure medications, such as cannabidiol and fenfluramine, is still scarce.

Optimal contraception strategies

Contraception choices in women with epilepsy of childbearing potential should be individualised, considering the potential interactions (appendix p 1–2), to minimise contraceptive failure and ensure optimal seizure control. Long-acting reversible contraceptives, including implants and intrauterine devices (IUDs) are the most effective.[48] Both copper and hormonal IUDs are safe for people with epilepsy of childbearing potential, as hormonal IUDs containing levonorgestrel interact minimally with antiseizure medications.[48] Individuals using enzyme-inducing antiseizure medications and oral contraceptives should use a higher dose of oral contraceptives or combine hormonal contraceptive methods with barrier methods, such as condoms with spermicide.[64]

Folic acid supplementation

Serum folate concentrations could potentially modulate the risk of antiseizure medication-associated fetal harm, since low folate and elevated homocysteine concentrations are common in patients using antiseizure medications.[65–67] Folate deficiency in the general population is linked to adverse outcomes, and are more frequent in antiseizure medication-exposed pregnancies.[66,65] Research on folic acid supplementation in pregnant people taking antiseizure medications suggests potential benefits, including reduced risk of fetal loss, preterm birth, and neurodevelopmental outcomes.[68–70] However, these findings are not consistent across all studies.[21,26] Robust clinical evidence for the prevention of antiseizure medication-associated major congenital anomaly is scarce,[14] with most studies not showing a benefit of supplementation.[4,70] Delayed initiation of folic acid supplements is common[50,70,71] and could mask any positive effect.[70] One case–control study on neural tube defects reported a reduced risk when folic acid was taken before 28 days after the last menstrual period in pregnancies exposed to antiseizure medications.[72]

Studies have raised concerns about high-dose folic acid and poorer child cognitive development,[73–75] with the suggestion of a U-shaped relationship where both too low and too high concentrations could be harmful.[74,75] Additionally, in one large Nordic registry-based cohort, prescriptions of 1 mg or more were linked to an increased risk of cancer in children of mothers with epilepsy[6] and a small increased risk of maternal cancer;[76] however, replication is required to confirm these observations.

The optimal folic acid dose and treatment duration in people with epilepsy of childbearing potential using antiseizure medications are unknown.[4] WHO recommends that all people of childbearing potential maintain red blood cell folate concentrations of more than 906 nmol/L (corresponding serum folate of 28–30 nmol/L)[67] and use 0·4 mg daily folic acid supplements for 2–3 months before conception until the 12th week of pregnancy to prevent neural tube defects.[67] To ensure sufficient folate status in the periconceptional period, the International League Against Epilepsy additionally advises women of childbearing potential using antiseizure medications to take at least 0·4 mg of folic acid daily, regardless of pregnancy plans.[2] The American Academy of Neurology recommends at least 0·4 mg daily preconceptionally and continued throughout pregnancy.[4] Others suggest doses up to 5 mg,[51,77] and prescribing practices vary internationally.[50,70,71] Given the uncertain risk–benefit profile, more recent recommendations suggest lowering doses to 0·8–3 mg[78–80] or advocate for individualised doses based on personal risk factors for folate deficiency (eg, low folate status, supplement non-adherence, family history of major congenital anomaly, *MTHFR* rs1801133 TT polymorphisms, obesity, smoking, diabetes, or use of valproate, carbamazepine, or high-dose antiseizure medications).[66] Although data on a personalised approached are scarce, tailored folate supplementation to target serum folate concentrations (28–30 µmol/L or red blood cell folate >906 nmol/L) might reduce neural tube defects and avoid concentrations in excess.[81] Since low adherence to folic acid recommendations is common,[50,70,71] preconception folate measurements could be helpful to identify individuals who would benefit from intensified counselling or higher doses. B12 concentrations should also be measured before initiating high-dose folic acid to avoid masking deficiencies, as it has been shown that elevated folic acid concentrations in the context of low B12 are detrimental to synaptic development in fetal animals.[82]

Management of epilepsy during pregnancy

Physiological changes associated with pregnancy lead to changes in the pharmacokinetics of some antiseizure medications.[7] Serum concentrations of some antiseizure medications should be monitored across the preconception, pregnancy, and postpartum periods.[4] Monitoring is especially important in people using antiseizure medications with a known pregnancy-associated drop in serum concentrations, such as lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and zonisamide,[7] or those who are already taking the lowest, effective antiseizure medication dose at the start of their pregnancy, had previous severe or injurious seizures, or had previous breakthrough seizures after missing doses.[2] The MONEAD prospective, observational cohort study, including 1087 women with epilepsy in the USA, showed that changes in clearance for some antiseizure medications, such as lamotrigine, are seen as early as in the third week of pregnancy, with clearance increasing by 50% by the end of the first trimester.[7] However, further investigation of this cohort revealed that 9% of women taking lamotrigine did not have increased clearance.[83] The greatest increase in levetiracetam clearance also appears to occur in the first trimester, with smaller changes throughout the second and third trimesters and a decrease postpartum, requiring a rapid reduction after delivery.[4,7,84,85] Unbound valproate should be monitored during pregnancy due to the substantial pharmacokinetic variability observed during this period. The unbound fraction is the pharmacologically active substance, responsible for both therapeutic efficacy and potential teratogenic effects. Physiological changes in pregnancy, such as increased plasma volume and decreased serum albumin, can lead to higher concentrations of unbound valproate, making total valproate concentration measurements potentially misleading.[85]

Management during labour

With optimal care, 90% of children born to people with epilepsy are healthy at birth.[27] However, women with epilepsy of childbearing potential still face increased risks during pregnancy and childbirth, including complications such as hypertensive disorders, preterm labour, placental abruption, gestational diabetes, anaemia, premature rupture of membranes, and mortality.[3,27,86] In a systematic review and meta-analysis including 76 studies, neonates born to women with epilepsy had higher odds of being small for gestational age, low birthweight (<2500 g), a 1-min and 5-min Apgar score of less than 8, and neonatal or infant death.[86] Other complications such as preterm birth, fetal distress, neonatal hypoglycaemia, neonatal infection, and respiratory distress syndrome have also been reported.[3,27,86]

Carefully developed, cross specialty birth plans are therefore imperative: caesarean section can be considered for those with high-frequency seizures during pregnancy and high seizure risk during labour;[87] epidural anaesthesia can reduce seizure risk by alleviating stress and pain;[87] hyperventilation and maternal exhaustion should be avoided to prevent seizure exacerbation;[87] antiseizure medications should be taken regularly during labour and venous access should be ready for timely benzodiazepine or antiseizure medication administration, if required;[88] and continuous cardiotocography and fetal monitoring are essential to prevent complications linked to fetal hypoxia, and the birthing facility should be equipped for maternal and neonatal resuscitation.[62,87]

Breastfeeding management during postpartum

Although the benefits of breastfeeding for both mother and child are widely acknowledged, the initiation and duration rates of breastfeeding are still much lower in

	Milk to maternal serum concentration ratio (number of cases, [average; range])	Infant to maternal serum concentration ratio (number of cases, [average; range])	Serum concentration in infant (%)	Adverse effects on breastfed infant
Brivaracetam	2 (0·61–0·75)	2 (<LOQ–0·20)	Approximately 30% of maternal serum concentrations	None reported
Carbamazepine	72 (<0·5; 0·13–1·5)	66 (<0·1; 0·04–0·7)	≤10% of maternal serum concentrations	1 case of hepatic dysfunction, 1 case of vomiting and regurgitation, and 1 case of cholestatic hepatitis
Clonazepam	1 (0·35)	1 (0·2)	≤10% of maternal serum concentrations	None reported
Ethosuximide	16 (0·9; 0·8–1·0)	12 (0·3–0·75)	30–100% of maternal serum concentrations	1 case of sedation, 1 case of poor suckling, and 1 case of weight gain
Gabapentin	7 (1·0; 0·7–1·3)	7 (0·1)	≤10% of maternal serum concentrations	None reported
Lacosamide	2 (0·1–0·83)	2 (0·05–0·27)	Approximately 30% of maternal serum concentrations	None reported
Kohn et al, 2020[94]	1 (0·5)	1 (0·22)	..	None reported
Kacirova et al, 2022[99]	6 (0·77–0·93)	6 (0·16 -0·35)	..	None reported
Lamotrigine	92 (0·6–0·7; 0·18–1·4)	166 (0·3; 0·2–0·9)	Approximately 30% of maternal serum concentrations	1 case of episodes of apnoea and 1 case of anaemia
Kacirova et al[99]	158 (0·60; 0·18–1·22)	143 (0·60; 0·13–2·43)	..	..
Levetiracetam	82 (1·0; 0·58–1·79)	121 (0·1; <71–0·71)	≤10% of maternal serum concentrations	1 case of hypotonia and 3 cases of sedation
Dinavitser et al[98]	14 (0·88; 0·23–1·1)	..	..	..
Oxcarbazepine	3 (0·5–0·8)	8 (<LOQ–0·009)	≤10%of maternal serum concentrations	None reported
Perampanel	1 (0·1–0·17)	1 (0·16–0·27)	Approximately 30% of maternal serum concentrations	None reported
Kacirova et al, 2022[100]	6 (0·01–0·10)	6 (0·36)	..	None reported
Phenobarbital	37 (0·40; 0·16–0·70)	24 (0·8–0·9)	30–100% of maternal serum concentrations	1 case of lethargy with high concentrations
Phenytoin	15 (0·13–0·18)	6 (<LOQ–0·01)	≤10% of maternal serum concentrations	None reported
Pregabalin	10 (0·76)	0	None reported	None reported
Primidone	36 (0·41; 0·48–1·1)	0	None reported	2 cases of prolonged feeding difficulties and 2 cases of sedation
Topiramate	31 (1·0; 0·62–2·43)	28 (0·25; <LOQ–0·7)	Approximately 30% of maternal serum concentrations	1 case of diarrhoea
Valproate	56 (0·025; 0·01–0·1)	34 (0·1; <LOQ–0·25)	≤10% of maternal serum concentrations	None reported
Kacirova et al[97]	90 (0·01–0·22)	78 (0·01 -1·61)	..	None reported
Zonisamide	3 (0·7–1·03)	5 (0·44; 0·17–1·25)	30–100% of maternal serum concentrations	None reported
Kacirova et al[96,100]	6 (0·76–1·26)	6 (0·44–0·85)	..	None reported

No data available for cenobamate, eslicarbazepine-acetate, everolimus, felbamate, fenfluoramine, pregabalin, rufinamide, retigabine, stiripentol, tiagabine, vigabatrin or clobazam, therefore careful counselling is required for people with epilepsy taking these medications who wish to consider breastfeeding. Data in the table are from Tomson and colleagues, 2022.[93] The other references in the table were published after that review. LOQ=level of quantification.

Table 2: **Antiseizure medication concentrations in maternal and infant samples and adverse event data for infants**

people with epilepsy than in women without epilepsy.[26,89,90] Socioeconomic limitations, fear of seizures due to sleep deprivation, and concern over transfer of antiseizure medications to the baby via breastmilk are the main causes.[26,91] These causes are exacerbated by insufficient information, inconsistent safety advice from health-care providers, or discouragement from social support networks.[92] However, counselling before and after delivery with lactation consultants improves breastfeeding initiation and continuation rates.[89]

Concentrations of antiseizure medications are detectable in breastmilk and, consequently, breastfeeding infants.[90] The transfer of antiseizure medications to the infant is influenced by the chemical properties of the drug, the maternal serum drug concentration, and the infant's absorption and elimination capabilities.[93] However, precise measurement of the infant's drug exposure via breastmilk is challenging.[93] Comprehensive data on antiseizure medication concentrations in breastfed infants are available only for some medications, whereas information on others is limited to case reports or case series in ten mother–child pairs or fewer, or completely absent (table 2).[93–95] For most antiseizure medications, including carbamazepine, gabapentin, levetiracetam, oxcarbazepine, phenytoin, valproate, and clonazepam, very low to low concentrations in breastfed infants are reported (≤10% of maternal serum concentrations),[96,97] but individual concentrations can vary.[98] Infants exposed to other antiseizure medications such as lamotrigine[99] or topiramate can have up to 30% of maternal serum concentrations. Among the studied antiseizure medications, ethosuximide, phenobarbital, and zonisamide have been associated with high infant concentrations (30–100% of maternal serum

concentrations; table 2).[90,93,96,100] For many newer antiseizure medications, data on breastmilk concentrations or infant plasma concentrations are absent.

The most reported acute side-effects in infants exposed to antiseizure medications via breastmilk are drowsiness, sedation, absent suck, cyanosis, bradycardia, vomiting, and diarrhoea.[93] These side-effects are rare, but if suspected, measuring antiseizure medication concentrations in the infant should be considered regardless of which antiseizure medication the mother is taking. Exposure can be reduced by combining breastfeeding with formula milk.

Little is known about long-term effects, with the exception of lamotrigine, levetiracetam, carbamazepine, phenytoin, and valproate, for which there are some supportive data that breastfeeding does not adversely affect neurodevelopment up to 6 years of age (table 3).[20,26,35,101] Although data are minimal, there is agreement, based on current information, that the benefits of breastfeeding outweigh the likely small risk of adverse antiseizure medication effects in the infant, and breastfeeding should be encouraged in people with epilepsy.[51,93] Therefore, the decision to breastfeed should be based on the person's feeding preferences, an evaluation of the specific antiseizure medication, dosage, serum concentrations, and infant health status. However, parents should be informed about signs of adverse effects from antiseizure medications.

	Number of participants	Key findings
Meador et al (2010, 2013):[20,101] prospective, observational, multicentre study		
Carbamazepine	47	Higher IQ and enhanced verbal abilities at age 6 years in breastfed children
Lamotrigine	61	As above
Phenytoin	37	As above
Valproate	36	As above
Veiby et al (2013):[102] prospective, cohort study in Norway		
Carbamazepine	48	Continuous breastfeeding linked to less impaired development at age 6 months and 18 months compared with no breastfeeding, with similar development at 36 months to those who had discontinued earlier
Lamotrigine	71	As above
Valproate	27	As above
Lattanzi et al (2017):[95] case series		
Lacosamide	3	Normal milestones at age 18 months, 24 months, and 36 months
Meador et al (2025):[35] prospective, observational, multicentre study		
Lamotrigine	97	Development at 2 years of age did not differ between children of women with epilepsy taking antiseizure medications and children of women without epilepsy
Levetiracetam	70	As above
Bromley et al (2023):[26] prospective, observational, multicentre study		
Lamotrigine	106	Development at age 2 years did not differ (regarding cognitive, language, or motor developmental scores) compared with the control group
Levetiracetam	70	As above

IQ=intelligence quotient.

Table 3: **Studies of neurodevelopmental outcomes in breastfed infants of mothers taking antiseizure medications**

Epilepsy care in the postpartum period

In the postpartum period, women with epilepsy face challenges including antiseizure medication adjustments, sleep deprivation, and seizure-related concerns. Perinatal depression and anxiety are more frequent in both mothers and fathers with epilepsy than in other parents.[103,104] Factors associated with major depressive episodes during pregnancy and postpartum include frequent seizures, antiseizure medications polytherapy, unplanned pregnancy, and a history of mood disorders.[104] These findings highlight the need for enhanced screening and management of anxiety and depression in pregnant and postpartum women with epilepsy (panel 2).

Two studies underline that postpartum women with epilepsy are at higher risk for health issues[105,106] and mortality than the general postpartum population.[3] The management of antiseizure medications in the postpartum period requires diligent consideration and monitoring. Following birth, antiseizure medication dosages can be reduced by 50% within 3 days, with a return to preconception concentrations[107] within 3 weeks.[2,107] Specific antiseizure medications, such as levetiracetam, eslicarbazepine, lamotrigine, and topiramate, require close monitoring during pregnancy and the postpartum period.[107] Maintaining slightly elevated antiseizure medication doses can help mitigate the effects of sleep deprivation, stress, and increased bodyweight, but should be tailored to the individual situation and seizure risk.[107] Patients should be vigilant of side-effects of higher antiseizure medication concentrations, including diplopia, dizziness, ataxia, and the risk of breakthrough seizures. Several adaptations are also required for new parents with epilepsy (panel 2).

Challenges in low-resource settings

The burden of epilepsy is greater in LMICs than in high-income countries due to a higher prevalence and reduced access to specialist care. Treatment options are often restricted to low cost antiseizure medications that can be afforded by public health systems, such as carbamazepine, phenytoin, and phenobarbital, and these drugs can still have low availability.[49,50] For example, in a study from low-resource areas in China, antiseizure medications were among the least available medications, with phenytoin in stock at 1% of public hospitals and carbamazepine in stock at 5% of public hospitals.[108] For people with epilepsy of childbearing potential, these differences often become more evident. The scarcity of ideal contraceptive methods, such as IUDs, occurs both due to restricted access and religious barriers. The use of phenobarbital, phenytoin, and carbamazepine can interfere with the metabolism of oral contraceptives, leading to unintended pregnancies (appendix pp 1–2).

Panel 2: Postpartum care considerations

Preventing seizure triggers

- Sleep deprivation in the postpartum period increases seizure risk; stable sleep patterns and medication adherence are essential
- Shared feeding duties using pumped breastmilk or formula can increase opportunities to sleep and decrease risk of early morning seizures, such as myoclonias, which could potentially harm the child

Reducing impact on mental health

- Perinatal depression and anxiety are more frequent in both mothers and fathers with epilepsy than in other parents;[103,104] previous psychiatric disorders and epilepsy severity are strong predictors
- Ensure that postnatal care teams are aware of the increased risk for poor mental health for people with epilepsy[99,100]
- Screening for peripartum depression should be done during pregnancy and in the postpartum period with validated tools such as the Patient Health Questionnaire-9 (9 questions) and the Edinburgh Postnatal Depression Screen (10 questions)
- Provide advice and guidance regarding strategies protective of mental health in the postpartum period and the health professionals that should be contacted if difficulties start

Infant care and safety practices

- Use cots on wheels for indoor transport and prams for outdoor mobility
- Choose lifts over stairs to minimise risks
- Do nappy changes on the floor and use facecloths instead of bathing to reduce potential hazards

Safe breastfeeding practices

- Breastfeed in a secure, comfortable environment (eg, the centre of a large bed)
- Take antiseizure medications immediately after breastfeeding or before the infant's longest sleep period to reduce exposure
- For high antiseizure medication concentrations in the infant's serum that cause sedation, introduce formula feeding alongside breastfeeding and consider regular serum monitoring for medications with scarce safety data

Referral for child health or developmental concerns

- Refer children with suspected physical or neurodevelopmental concerns or high-risk in-utero antiseizure medication exposure (figure 2) to multidisciplinary teams with experience of fetal exposure conditions (ie, fetal valproate spectrum disorder)[29]

Medications that are frequently available and affordable, and therefore used more in LMICs, appear to have higher associated risks of poor outcomes in offspring. Valproate, despite its high teratogenic potential, is commonly used by people with epilepsy of childbearing potential in LMICs due to its low cost, poor availability of alternative effective antiseizure medications, and little access to adequate monitoring.[1,49,50] Valproate was added to the WHO essential medicines list in 1977, and now is included in 93% of national essential medicines lists. However, lamotrigine was not included in the WHO essential medicines list until 2017, and levetiracetam was not included until 2023,[28] despite these being safer alternatives (figure 2), and thus they are not yet readily available and affordable on a sustainable basis in many countries.[55,109] For example, in 2022, valproate was available in 95% of public and private pharmacies in Ethiopia, whereas lamotrigine was dispensed in only 22% of public and private pharmacies and at a higher cost.[50] By avoiding higher cost antiseizure medications, LMICs are inadvertently increasing the health, social, and educational costs associated with caring for children with fetal exposure-related conditions. When there is no alternative to high risk antiseizure medications, risk counselling and shared decision making is crucial and, when possible, monotherapy must be used at the lowest effective dose.

Search strategy and selection criteria

References for this Review were identified by searches of MEDLINE, Embase, and PsycINFO via OVID between Jan 1, 2019, and Jan 1, 2025, and references from relevant articles. The search terms included "epilepsy", "seizure", "antiseizure", "anticonvulsant", "antiepileptic", "pregnan$", "utero, "fetal", "neurodevelopment$", "neurocognitive", "development$", "neuropsycholog$", "anomaly", "malformation", "growth", "breastfeeding", "contraception", "birth", and "postnatal". There were no language restrictions. The final reference list was generated based on relevance to the topics covered in this Review.

Conclusions and future directions

Important challenges occur at reproductive age for people with epilepsy, and clinical knowledge of optimal care is continually evolving. Despite life-altering implications for people with epilepsy, clinical care is often compromised by a scarcity of information for many antiseizure medications regarding contraceptive interactions, alterations in clearance, and offspring outcomes. An absence of risk evidence should not be assumed to be evidence of safety. Therefore, there is an urgent need for additional research and an improved pharmacovigilance strategy alongside an equally urgent need to optimise care for people with epilepsy in all stages of their reproductive journey.

Improvement will require collaborative efforts from multiple stakeholders, including national and international initiatives with different methodological frameworks (clinical and epidemiological). Harmonised protocols facilitating pooled data analyses are essential to provide more robust short-term and long-term risk assessments, and also to assess safety and efficacy of high dose folic acid supplementation.

Finally, we call for inclusive research into the reproductive risks associated with epilepsy that recognises the diverse experiences of all individuals with epilepsy, regardless of gender identity.

Contributors

Conceptualisation: RLB and MHB. Project administration and literature search: RLB. Literature review, writing the original draft, figures and tables, and reviewing and editing the draft: MHB, CC, BN, and RLB.

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References
1 WHO. Epilepsy: a public health imperative. World Health Organization, 2019.
2 Tomson T, Battino D, Bromley R, et al. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. *Epileptic Disord* 2019; **21:** 497–517.
3 Razaz N, Igland J, Bjørk MH, et al. Risk of perinatal and maternal morbidity and mortality among pregnant women with epilepsy. *JAMA Neurol* 2024; **81:** 985–95.
4 Pack AM, Oskoui M, Williams Roberson S, et al. Teratogenesis, perinatal, and neurodevelopmental outcomes after in utero exposure to antiseizure medication: practice guideline from the AAN, AES, and SMFM. *Neurology* 2024; **102:** e209279.
5 European Medicines Agency. Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures. 2024. https://www.ema.europa.eu/en/news/potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproate-medicines-prac-recommends-precautionary-measures (accessed March 30, 2025)
6 Vegrim HM, Dreier JW, Alvestad S, et al. Cancer Risk in children of mothers with epilepsy and high-dose folic acid use during pregnancy. *JAMA Neurol* 2022; **79:** 1130–38.
7 Pennell PB, Karanam A, Meador KJ, et al. Antiseizure medication concentrations during pregnancy: results from the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Study. *JAMA Neurol* 2022; **79:** 370–79.
8 Herzog AG, Mandle HB, Cahill KE, Fowler KM, Hauser WA. Predictors of unintended pregnancy in women with epilepsy. *Neurology* 2017; **88:** 728–33.
9 Johnson EL, Burke AE, Wang A, Pennell PB. Unintended pregnancy, prenatal care, newborn outcomes, and breastfeeding in women with epilepsy. *Neurology* 2018; **91:** e1031–39.
10 Tomson T, Battino D, Bonizzoni E, et al. Withdrawal of valproic acid treatment during pregnancy and seizure outcome: observations from EURAP. *Epilepsia* 2016; **57:** e173–77.
11 Elwyn G, Durand MA, Song J, et al. A three-talk model for shared decision making: multistage consultation process. *BMJ* 2017; **359:** j4891.
12 Bromley RL, Bickle Graz M, Bluett-Duncan M, et al. Expert consensus on neurodevelopmental outcomes in pregnancy pharmacovigilance studies. *Front Pharmacol* 2023; **14:** 1094698.
13 Bromley R, Adab N, Bluett-Duncan M, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev* 2023; **8:** CD010224.
14 Battino D, Tomson T, Bonizzoni E, et al. Risk of major congenital malformations and exposure to antiseizure medication monotherapy. *JAMA Neurol* 2024; **81:** 481–89.
15 Adams J, Janulewicz PA, Macklin EA, et al. Neuropsychological effects in children exposed to anticonvulsant monotherapy during gestation: phenobarbital, carbamazepine, and phenytoin. *Epilepsy Behav* 2022; **127:** 108533.
16 Cohen JM, Alvestad S, Cesta CE, et al. Comparative safety of antiseizure medication monotherapy for major malformations. *Annals Neurol* 2023; **93:** 551–62.
17 Hernández-Díaz S, Mittendorf R, Smith CR, Hauser WA, Yerby M, Holmes LB. Association between topiramate and zonisamide use during pregnancy and low birth weight. *Obstet Gynecol* 2014; **123:** 21–28.
18 Christensen J, Zoega H, Leinonen MK, et al. Prenatal exposure to antiseizure medications and fetal growth: a population-based cohort study from the Nordic countries. *Lancet Reg Health Eur* 2024; **38:** 100849.
19 Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol* 2014; **261:** 579–88.
20 Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013; **12:** 244–52.
21 Baker GA, Bromley RL, Briggs M, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. *Neurology* 2015; **84:** 382–90.
22 Bjørk MH, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. *JAMA Neurol* 2022; **79:** 672–81.
23 Dreier JW, Bjørk MH, Alvestad S, et al. Prenatal exposure to antiseizure medication and incidence of childhood- and adolescence-onset psychiatric disorders. *JAMA Neurol* 2023; **80:** 568–77.
24 Hernández-Díaz S, Straub L, Bateman BT, et al. Risk of autism after prenatal topiramate, valproate, or lamotrigine exposure. *N Engl J Med* 2024; **390:** 1069–79.
25 Husebye ESN, Gilhus NE, Spigset O, Daltveit AK, Bjørk MH. Language impairment in children aged 5 and 8 years after antiepileptic drug exposure in utero - the Norwegian Mother and Child Cohort Study. *Eur J Neurol* 2020; **27:** 667–75.
26 Bromley RL, Bullen P, Campbell E, et al. Neurodevelopment of babies born to mothers with epilepsy: a prospective observational cohort study. *Epilepsia* 2023; **64:** 2454–71.
27 Kuang H, Li Y, Lu Y, Zhang L, Wei L, Wu Y. Reproductive and fetal outcomes in women with epilepsy: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2024; **37:** 2351196.
28 World Health Organization. Essential medicines list. https://list.essentialmeds.org/medicines (accessed Nov 12, 2024).
29 Clayton-Smith J, Bromley R, Dean J, et al. Diagnosis and management of individuals with fetal valproate spectrum disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability. *Orphanet J Rare Dis* 2019; **14:** 180.
30 Choi CS, Gonzales EL, Kim KC, et al. The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. *Sci Rep* 2016; **6:** 36250.
31 Martin M, Hill C, Bewley S, MacLennan AH, Braillon A. Transgenerational adverse effects of valproate? A patient report from 90 affected families. *Birth Defects Res* 2022; **114:** 13–16.
32 Gov.UK. Topiramate (Topamax): introduction of new safety measures, including a pregnancy prevention programme. 2024. https://www.gov.uk/drug-safety-update/topiramate-topamax-introduction-of-new-safety-measures-including-a-pregnancy-prevention-programme (accessed March 4, 2025).
33 European Medicines Agency. New measures to avoid topiramate exposure in pregnancy. Further restrictions on use; pregnancy prevention programme to be put in place. https://www.ema.europa.eu/en/medicines/human/referrals/topiramate (accessed May 28, 2024).
34 Madley-Dowd P, Ahlqvist VH, Forbes H, et al. Antiseizure medication use during pregnancy and children's neurodevelopmental outcomes. *Nat Commun* 2024; **15:** 9640.

35 Meador KJ, Cohen MJ, Loring DW, et al. Neuropsychological outcomes in 6-year-old children of women with epilepsy: a prospective nonrandomized clinical trial. *JAMA Neurol* 2025; **82:** 30–39.

36 Conei D, Rojas M, Santamaría L, Risopatrón J. Valproic acid during pregnancy decrease the number of spermatogenic cells and testicular volume in the offspring of mice: stereological quantification. *Histol Histopathol* 2021; **36:** 1189–98.

37 European Medicines Agency. PRAC non-interventional imposed PASS final study report assessment report: valproate and related substances (sodium valproate, valproic acid, valproate semisodium, valpromide, valproate magnesium). 2024, European Medicines Agency.

38 European Medicines Agency. A post-authorization safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring—a population-based retrospective study. 2023, European Medicines Agency.

39 Christensen J, Trabjerg BB, Dreier JW. Valproate use during spermatogenesis and risk to offspring. *JAMA Netw Open* 2024; **7:** e2414709.

40 Tomson T, Muraca G, Razaz N. Paternal exposure to antiepileptic drugs and offspring outcomes: a nationwide population-based cohort study in Sweden. *J Neurol Neurosurg Psychiatry* 2020; **91:** 907–13.

41 Gov.UK. Valproate use in men: as a precaution, men and their partners should use effective contraception. 2024. https://www.gov.uk/drug-safety-update/valproate-use-in-men-as-a-precaution-men-and-their-partners-should-use-effective-contraception#review-of-data-regarding-potential-risk-to-children-with-paternal-use-of-valproate (accessed Sept 29, 2024).

42 The Lancet Neurology. Reducing the uses of valproate: a controversial decision. *Lancet Neurol* 2024; **23:** 123.

43 Cave A. The prescription of valproate: risk of harm. *Lancet Neurol* 2024; **23:** 557.

44 Honybun E, Rayner G, Malpas CB, et al. Paternal exposure to antiseizure medications and offspring outcomes: a systematic review. *J Neurol Neurosurg Psychiatry* 2024; **96:** 15–25.

45 Garey JD, Damkier P, Scialli AR, et al. Paternal valproate treatment and risk of childhood neurodevelopmental disorders: precautionary regulatory measures are insufficiently substantiated. *Birth Defects Res* 2024; **116:** e2392.

46 Yang F, Yuan W, Liang H, et al. Preconceptional paternal antiepileptic drugs use and risk of congenital anomalies in offspring: a nationwide cohort study. *Eur J Epidemiol* 2019; **34:** 651–60.

47 Lamberink HJ, Otte WM, Geerts AT, et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *Lancet Neurol* 2017; **16:** 523–31.

48 King A, Gerard EE. Contraception, fecundity, and pregnancy in women with epilepsy: an update on recent literature. *Curr Opin Neurol* 2022; **35:** 161–68.

49 Menon S, Siewe Fodjo JN, Weckhuysen S, et al. Women with epilepsy in sub-Saharan Africa: a review of the reproductive health challenges and perspectives for management. *Seizure* 2019; **71:** 312–17.

50 Teuwen DE, Ndayisenga A, Garrez I, et al. Challenges to epilepsy management in Rwandan women living with epilepsy. *Eur J Neurol* 2024; **31:** e16254.

51 National Institute for Health and Care Excellence. Epilepsies in children, young people and adults. 2022, National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ng217/resources/epilepsies-in-children-young-people-and-adults-pdf-66143780239813 (accessed Jan 3, 2023).

52 Decker BM, Acton EK, Davis KA, Willis AW. Inconsistent reporting of drug-drug interactions for hormonal contraception and antiepileptic drugs - Implications for reproductive health for women with epilepsy. *Epilepsy Behav* 2021; **114:** 107626.

53 Dupont S, Vercueil L. Epilepsy and pregnancy: what should the neurologists do? *Rev Neurol* 2021; **177:** 168–79.

54 Weatherspoon S, Davis A, Keezer M, Zutshi D, Pack A. Dobbs versus Jackson: epilepsy, reproductive health, and abortion. *Epilepsy Curr* 2023; **23:** 211–16.

55 Persaud N, Jiang M, Shaikh R, et al. Comparison of essential medicines lists in 137 countries. *Bull World Health Organ* 2019; **97:** 394–404C.

56 Doose DR, Wang SS, Padmanabhan M, Schwabe S, Jacobs D, Bialer M. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. *Epilepsia* 2003; **44:** 540–49.

57 Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* 1997; **38:** 317–23.

58 Falcão A, Vaz-da-Silva M, Gama H, Nunes T, Almeida L, Soares-da-Silva P. Effect of eslicarbazepine acetate on the pharmacokinetics of a combined ethinylestradiol/levonorgestrel oral contraceptive in healthy women. *Epilepsy Res* 2013; **105:** 368–76.

59 Klosterskov Jensen P, Saano V, Haring P, Svenstrup B, Menge GP. Possible interaction between oxcarbazepine and an oral contraceptive. *Epilepsia* 1992; **33:** 1149–52.

60 Sidhu J, Job S, Singh S, Philipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol* 2006; **61:** 191–99.

61 Rauchenzauner M, Deichmann S, Pittschieler S, et al. Bidirectional interaction between oral contraception and lamotrigine in women with epilepsy - role of progestins. *Seizure* 2020; **74:** 89–92.

62 Darmawan KF, Panelli DM. Contemporary management of epilepsy in pregnancy. *Curr Opin Obstet Gynecol* 2023; **35:** 87–93.

63 Herzog AG, Blum AS, Farina EL, et al. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. *Neurology* 2009; **72:** 911–14.

64 Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking anticonvulsant therapy. *Contraception* 2011; **83:** 16–29.

65 Husebye ESN, Riedel B, Bjørke-Monsen AL, et al. Vitamin B status and association with antiseizure medication in pregnant women with epilepsy. *Epilepsia* 2021; **62:** 2968–80.

66 Wilson RD, O'Connor DL. Maternal folic acid and multivitamin supplementation: international clinical evidence with considerations for the prevention of folate-sensitive birth defects. *Prev Med Rep* 2021; **24:** 101617.

67 Cordero AM, Crider KS, Rogers LM, Cannon MJ, Berry RJ. Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects: World Health Organization guidelines. *MMWR Morb Mortal Wkly Rep* 2015; **64:** 421–23.

68 Meador KJ, Pennell PB, May RC, et al. Effects of periconceptional folate on cognition in children of women with epilepsy: NEAD study. *Neurology* 2020; **94:** e729–40.

69 Bjørk M, Riedel B, Spigset O, et al. Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero. *JAMA Neurol* 2018; **75:** 160–68.

70 Ban L, Fleming KM, Doyle P, et al. Congenital anomalies in children of mothers taking antiepileptic drugs with and without periconceptional high dose folic acid use: a population-based cohort study. *PLoS One* 2015; **10:** e0131130.

71 Vegrim HM, Dreier JW, Igland J, et al. Prescribing patterns for higher dose folic acid in pregnant women with epilepsy treated with antiseizure medication. *Epilepsia* 2024; **65:** 1698–708.

72 Petersen JM, Parker SE, Benedum CM, Mitchell AA, Tinker SC, Werler MM. Periconceptional folic acid and risk for neural tube defects among higher risk pregnancies. *Birth Defects Res* 2019; **111:** 1501–12.

73 Valera-Gran D, García de la Hera M, Navarrete-Muñoz EM, et al. Folic acid supplements during pregnancy and child psychomotor development after the first year of life. *JAMA Pediatr* 2014; **168:** e142611.

74 Qu Y, Liu X, Lin S, et al. Maternal serum folate during pregnancy and congenital heart disease in offspring. *JAMA Netw Open* 2024; **7:** e2438747.

75 Raghavan R, Riley AW, Volk H, et al. maternal multivitamin intake, plasma folate and vitamin B_{12} levels and autism spectrum disorder risk in offspring. *Paediatr Perinat Epidemiol* 2018; **32:** 100–11.

76 Vegrim HM, Dreier JW, Igland J, et al. High-dose folic acid use and cancer risk in women who have given birth: a register-based cohort study. *Epilepsia* 2025; **66:** 75–88.

77 Tomson T, Battino D, Bromley R, et al. Global survey of guidelines for the management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. *Epilepsia Open* 2020; **5:** 366–70.

78 International League Against Epilepsy. Swiss League Against Epilepsy: revised folic acid RDA for women with epilepsy. 2023. https://www.ilae.org/news-and-media/news-about-ilae/swiss-league-against-epilepsy-revised-folic-acid-rda-for-women-with-epilepsy#:~:text=The%20Swiss%20League%20Against%20Epilepsy,unborn%20baby%20from%20developing%20abnormalities (accessed Sept 27, 2024).

79 Kinney MO, Craig JJ, Delanty N. Folic acid in women with epilepsy: prescribing advice. *Pract Neurol* 2024; **24:** 180–82.

80 Voinescu PE, Pennell PB, Meador K. Benefits and risks of periconceptional folic acid supplementation. *JAMA Neurol* 2023; **80:** 420–21.

81 Tam C, McKenna K, Goh YI, et al. Periconceptional folic acid supplementation: a new indication for therapeutic drug monitoring. *Ther Drug Monit* 2009; **31:** 319–26.

82 Tat L, Cannizzaro N, Schaaf Z, et al. Prenatal folic acid and vitamin B_{12} imbalance alter neuronal morphology and synaptic density in the mouse neocortex. *Commun Biol* 2023; **6:** 1133.

83 Karanam A, Pennell PB, Meador KJ, Long Y, Birnbaum AK. Characterization of lamotrigine disposition changes during and after pregnancy in women with epilepsy. *Pharmacotherapy* 2025; **45:** 33–42.

84 Fallik N, Trakhtenbroit I, Fahoum F, Goldstein L. Therapeutic drug monitoring in pregnancy: Levetiracetam. *Epilepsia* 2024; **65:** 1285–93.

85 Johannessen Landmark C, Farmen AH, Burns ML, et al. Pharmacokinetic variability of valproate during pregnancy—implications for the use of therapeutic drug monitoring. *Epilepsy Res* 2018; **141:** 31–37.

86 Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *Lancet* 2015; **386:** 1845–52.

87 Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. Epilepsy and pregnancy: an obstetric perspective. *Am J Obstet Gynecol* 2004; **190:** 371–79.

88 Nucera B, Brigo F, Trinka E, Kalss G. Treatment and care of women with epilepsy before, during, and after pregnancy: a practical guide. *Ther Adv Neurol Disord* 2022; **15:** 17562864221101687.

89 Eden A, Aboulatta L, Derksen S, Eltonsy S. Rates and determinants of breastfeeding initiation in women with and without epilepsy: a 25-year study. *Seizure* 2024; **121:** 30–37.

90 Birnbaum AK, Meador KJ, Karanam A, et al. Antiepileptic drug exposure in infants of breastfeeding mothers with epilepsy. *JAMA Neurol* 2020; **77:** 441–50.

91 Dyson L, McCormick F, Renfrew MJ. Interventions for promoting the initiation of breastfeeding. *Cochrane Database Syst Rev* 2005; **18:** CD001688.

92 Egawa M, Hara K, Ikeda M, et al. Role of obstetricians in promoting pregnancy-related knowledge among women with epilepsy in Japan. *Epilepsy Behav* 2020; **111:** 107176.

93 Tomson T, Battino D, Bromley R, et al. Breastfeeding while on treatment with antiseizure medications: a systematic review from the ILAE Women Task Force. *Epileptic Disord* 2022; **24:** 1020–32.

94 Kohn E, Dinavitser N, Gandelman-Marton R, et al. Lacosamide levels in blood and breastmilk during pregnancy and lactation: a case report. *Reprod Toxicol* 2020; **97:** 9–10.

95 Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Lacosamide during pregnancy and breastfeeding. *Neurol Neurochir Pol* 2017; **51:** 266–69.

96 Shawahna R, Zaid L. Concentrations of antiseizure medications in breast milk of lactating women with epilepsy: a systematic review with qualitative synthesis. *Seizure* 2022; **98:** 57–70.

97 Kacirova I, Grundmann M, Brozmanova H. Valproic acid concentrations in mothers, colostrum and breastfed infants during the early postpartum period: comparison with concentrations determined during delivery and in the mature milk period. *Pharmaceutics* 2021; **13:** 2074.

98 Dinavitser N, Kohn E, Berlin M, et al. Levetiracetam in lactation: How much is excreted into human breast milk? *Br J Clin Pharmacol* 2022; **88:** 199–205.

99 Kacirova I, Grundmann M, Brozmanova H. Monitoring of lamotrigine concentrations in mothers, colostrum, and breastfed newborns during the early postpartum period. *Biomed Pharmacother* 2022; **151:** 113167.

100 Kacirova I, Urinovska R, Grundmann M. Therapeutic monitoring of lacosamide, perampanel, and zonisamide during breastfeeding. *Epilepsy Res* 2024; **199:** 107264.

101 Meador KJ, Baker GA, Browning N, et al. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology* 2010; **75:** 1954–60.

102 Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. *JAMA Neurol* 2013; **70:** 1367–74.

103 Reiter SF, Veiby G, Bjørk MH, Engelsen BA, Daltveit AK, Gilhus NE. Psychiatric comorbidity, social aspects and quality of life in a population-based cohort of expecting fathers with epilepsy. *PLoS One* 2015; **10:** e0144159.

104 Meador KJ, Stowe ZN, Brown C, et al. Prospective cohort study of depression during pregnancy and the postpartum period in women with epilepsy vs control groups. *Neurology* 2022; **99:** e1573–83.

105 Darmawan KF, Leonard SA, Meador K, et al. Increased rates of postpartum emergency department visits and inpatient readmissions in people with epilepsy. *Am J Obstet Gynecol* 2023; **228:** S163.

106 Decker BM, Thibault D, Davis KA, Willis AW. A nationwide analysis of maternal morbidity and acute postpartum readmissions in women with epilepsy. *Epilepsy Behav* 2021; **117:** 107874.

107 Arfman IJ, Wammes-van der Heijden EA, Ter Horst PGJ, Lambrechts DA, Wegner I, Touw DJ. Therapeutic drug monitoring of antiepileptic drugs in women with epilepsy before, during, and after pregnancy. *Clin Pharmacokinet* 2020; **59:** 427–45.

108 Xu R, Li S, Lv X, Xie X. Prices, availability, and affordability of national essential medicines in public primary hospitals: a cross-sectional survey in poverty-stricken rural areas in China. *Int J Health Plann Manage* 2020; **35:** 545–57.

109 Hailemariam FH, Shifa M, Kassaw C. Availability, price, and affordability of antiseizure medicines in Addis Ababa, Ethiopia. *Epilepsia Open* 2023; **8:** 1123–32.