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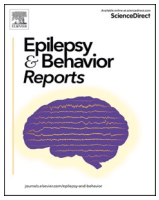

Management of epilepsy in pregnancy: What we still need to learn

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ABSTRACT

Safe pregnancies have been a major concern for women with epilepsy. With more than 50 years of research, we have learned that antiseizure medications (ASMs) differ in their teratogenic risk. Valproate is associated with greater risks for malformations and adverse neurodevelopmental outcomes than other ASMs. Furthermore, seizure control is important for maternal health in pregnancy and it can be affected by a decline in serum concentrations of many ASMs during pregnancy.

However, significant knowledge gaps remain. First, there is insufficient evidence about the relative teratogenic risks of most newer generation ASMs, as well as diverse ASM combinations. Similarly, information on gestation-induced changes in maternal serum levels and transfer into breastmilk is inadequate for the majority of the newer ASMs. Further, the optimal dose of folate supplementation remains unknown for women with epilepsy. Finally, most of previous studies on epilepsy and pregnancy come from Europe or North America. Efforts should be made to include more countries in collaboration with existing prospective epilepsy and pregnancy studies to increase the cohort size while at the same time enhancing the generalizability of the results. Large countries, such as China, present great potential to shorten the time to obtain answers to important unsolved questions.

1. Introduction

Safe pregnancies have been a major concern for the approximately 15 million women with epilepsy that are of child-bearing age in the world. Safety issues include the risk for obstetrical and perinatal complications, offspring outcomes, as well as maternal seizure control. More than 50 years ago, the first article reported a link between maternal exposure to antiseizure medications (ASMs) and congenital abnormalities in offspring [1]. Since then, numerous studies have been addressing the issues related to the management of epilepsy in pregnancy with various methodologies. These include prospective single center or multicenter cohort studies, population-based studies utilizing administrative national registers, and specific epilepsy and pregnancy registries [2].

However, there are still significant knowledge gaps. Currently, we have insufficient evidence regarding the safety of most of the newer ASMs during pregnancy. Additionally, the optimal dosage of folic acid supplementation for pregnant women with epilepsy remains unknown. And such issues could only be addressed through large-scale multicenter clinical studies. Past experience has shown that obtaining sufficient evidence requires a significant amount of time. In this regard, countries with large population such as China could play an potential role in shortening the time to obtain answers.

2. What we have learned so far

Studies have confirmed an increased prevalence of major congenital malformations (MCM) in offspring of women with epilepsy, which is mainly related to exposure to ASMs [2]. We have also learned that ASMs differ in the overall risk of teratogenic effects and also in the types of teratogenic outcomes, including growth restrictions, MCMs, and neurodevelopmental outcomes. Overall, the risk of teratogenic effects such as MCMs and adverse neurodevelopmental outcomes including autism spectrum disorders and intellectual disabilities, is greater with valproate and topiramate than with other ASMs including carbamazepine, lamotrigine, and levetiracetam [2–5]. These findings that have prompted regulatory bodies such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to introduce strict limitations for the use of valproate in women of childbearing age. Studies have also shown that teratogenic effects of some ASMs, in particular valproate, but also phenobarbital, carbamazepine, and lamotrigine are dose-dependent [3,8]. Research has demonstrated that opting for

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lamotrigine and levetiracetam instead of valproate before conception is linked to a lower occurrence of MCMs [9].

Studies have demonstrated that women with epilepsy had increased risks of maternal, fetal, and neonatal complications including miscarriage, preterm birth, antepartum and post-partum haemorrhage, hypertensive disorders and induction of labour [10,11]. Other studies have confirmed that epilepsy is a serious condition with increased mortality not least during pregnancy, with a maternal mortality 7–10 times than expected [12]. Effective treatment aiming at complete control of tonic-clonic seizures is thus important also during pregnancy despite the potential teratogenic risks associated with ASMs. Maintaining seizure control is complicated by the fact that pregnancy can have a profound effect on serum concentrations of ASMs. We have learned that this impact varies between ASMs, being most pronounced for lamotrigine, levetiracetam, oxcarbazepine, zonisamide and topiramate; but also that the decline in serum concentrations is unpredictable and varies between individual persons [13].

Another important lesson learned is that some ASMs, notably phenobarbital, probably lamotrigine and zonisamide, are extensively transferred into breastmilk but also that immediate or long-term adverse effects of breastfeeding are rare [14–16]. Given the benefits of breastfeeding to both mother and child, breastfeeding should be encouraged for women with epilepsy taking ASMs.

3. What we still need to learn

Important knowledge gaps persist, and new issues emerge over time. A significant reason is that there is limited knowledge about the use of many new ASMs during pregnancy [Drug Safety Update - GOV.UK (https://www.gov.uk)], [The North American Antiepileptic Drug Pregnancy Registry (aedpregnancyregistry.org)]. Experience has taught us that it takes decades from the introduction of a new ASM to the market before enough data is available to make a reasonable assessment of its safety during pregnancy. In the following we will discuss deficits in some specific relevant areas.

3.1. Risk for malformations with less frequently used ASMs in monotherapy

Sufficient information on relative risk of MCMs is available only for a few ASMs, including carbamazepine, lamotrigine, levetiracetam, valproate, phenobarbital, and possibly oxcarbazepine, and topiramate. Of these, lamotrigine, levetiracetam, and possibly oxcarbazepine appear to be the safest, whereas valproate and possibly topiramate are associated with a higher occurrence of MCMs [4,7]. For newer ASMs, gabapentin and zonisamide seems to be safe in pregnancy. However, for most ASMs introduced during the last 20 years, information is insufficient to determine to what extent they are associated with increased risk of MCMs [17,18].

These knowledge gaps are even more pronounced when it comes to the associations between specific MCMs and ASMs. The differentiation is very important as different types of MCMs, such as hypospadias and neural tube defects, have varying impacts on quality of life. While we know that the pattern of malformations differs for the most commonly used ASMs, much more information is needed to fully understand this aspect.

3.2. Intrauterine growth restrictions

Similar limitation discussed above also apply for intrauterine growth restrictions. Current data suggests that exposure to topiramate, and possibly also carbamazepine and zonisamide, may have adverse effects on body weight and head circumference [19,20]. However, data on most other newer generation ASMs are still lacking. Another area that requires further research is the extent to which ASM-induced intrauterine growth restrictions affect the postnatal development of children.

3.3. Risk for malformations with ASMs in combination therapy

Approximately 10–15 % of all pregnancies among women with epilepsy are exposed to ASMs in polytherapy. While polytherapy was previously thought to be associated with higher teratogenic risks than monotherapy, data from epilepsy and pregnancy registries suggest that the risk is more dependent on the type of ASM included in the combination therapy than the number of ASMs [21,22]. However, data comparing teratogenic risks between specific ASM combinations and between specific combinations and ASM monotherapy are limited. Such studies are more complicated than monotherapy comparisons since they may involve pharmacodynamic as well as pharmacokinetic interactions, change in levels of active metabolites etc. Nevertheless, they are becoming increasingly important as prescribers search for alternatives to valproate and topiramate monotherapy.

3.4. Neurodevelopmental outcomes

Our current understanding of the possible impact of intrauterine exposure to ASM on the neurodevelopment of the child is even more limited than with structural teratogenicity. Recent smaller prospective cohort studies with meticulous assessments of the offspring at school age, and nationwide register-based studies have consistently demonstrated that valproate exposure is associated with increased risks of lower IQ, autism spectrum disorders, and intellectual disabilities in children. More recent studies have also suggested a similar association with topiramate exposure [5,6,17]. However, it is only with lamotrigine and possibly carbamazepine that we have sufficient data to assume that they are reasonably safe to use in this regard. Data on levetiracetam are accumulating but so far less than for lamotrigine and carbamazepine. When it comes to other old or newer ASMs data is clearly insufficient.

More recently, administrative nationwide registers have been utilized for long-term follow-up until adolescence to evaluate the association between prenatal exposure to ASMs and psychiatric disorders [26]. Exposure to valproate was found to be associated with increased risks, and concerns were raised regarding topiramate. Levetiracetam, lamotrigine, carbamazepine, and oxcarbazepine appeared to be safe in this regard. Nevertheless, this study emphasizes the need for studies with extended follow-up to assess the safety of most ASMs currently in use, as data in this area are lacking.

3.5. Impact on outcomes of switches/withdrawals of ASMs during pregnancy

Prospective studies have demonstrated that switching ASM selection, particularly from valproate to lamotrigine or levetiracetam, is associated with a reduction in the prevalence of MCMs in the offspring [9]. However, these observations are based on women who have been on these less teratogenic medications before conception. Therefore, it is generally recommended that an ASM switch or withdrawal should be completed well in advance of pregnancy. Data on risks and benefits of similar changes during pregnancy are very limited. A study from EURAP indicated that the risk of tonic-clonic seizures increased significantly among women that withdraw or switch from valproate treatment during the first trimester [23]. However, it is largely unknown whether withdrawing a potentially teratogenic ASM when pregnancy is already established is associated with improved outcomes in the offspring. This is an extremely important knowledge gap since the majority of pregnancies among women with epilepsy are unplanned, and the question of drug discontinuation often arises when a woman on valproate realizes that she is pregnant.

3.6. Effects of maternal seizures on fetus

The commonly accepted strategy of using ASMs during pregnancy, despite their teratogenic potential, is based on the belief that poorly

controlled seizures pose a greater harm than the ASMs themselves. The maternal risks with uncontrolled seizures are well known, and it has for instance been shown that maternal mortality is significantly increased among women with epilepsy [27]. However, there is limited knowledge about the fetal risks associated with maternal seizures, and this aspect has rarely been systematically studied in clinical studies. There is no evidence of an association between maternal seizures and the occurrence of MCMs in the offspring [4], whereas data are conflicting concerning the association with adverse neurodevelopmental outcomes. It is generally assumed that if there are adverse effects on the fetus, they are primarily related to tonic-clonic seizures, but possible risks associated with other types of maternal seizures have not been thoroughly assessed.

3.7. Effect of pregnancy on serum concentrations of ASMs

Serum concentrations of some ASMs decline significantly during pregnancy, which can be associated with a loss of seizure control [13]. Pronounced gestational alterations have been reported for lamotrigine, levetiracetam, lacosamide, oxcarbazepine, topiramate, and zonisamide, while active serum concentrations of carbamazepine and valproate remain fairly stable throughout pregnancy [13]. However, data on other ASMs such as brivaracetam, eslicarbazepine acetate, cannabidiol, perampanel, cenobamate, fenfluramine and more are lacking.

3.8. Breastfeeding

When known, ASM concentrations in children breastfed by mothers on treatment are generally very low. However, for some ASMs, notably phenobarbital and ethosuximide, the serum concentrations in the breastfed infant may reach levels comparable to those in the treated mother [14]. Data for lamotrigine have been variable, with ratios lower to 0.2 and higher to nearly 1 [14,24,25]. However, the average ratio is about 0.3. Zonisamide also may be transferred into breastmilk to a greater degree, but the data are quite limited [14]. A recent systematic review has highlighted that there are no data on levels in breastmilk or breastfed infants for most of the newer ASMs, including cannabidiol, cenobamate, eslicarbazepine-acetate, everolimus, felbamate, fenfluramine, rufinamide, and stiripentol [14]. Furthermore, little is known of possible long-term effects on children of exposure to ASMs through breastfeeding with the exception for lamotrigine, carbamazepine, phenytoin, and valproate, where no negative effects were noted on the child development at age six [19].

3.9. Folate supplementation

All women considering pregnancy are usually recommended a folate supplementation of 0.4 mg daily. However, those with risk factors for neural tube defects in the offspring are often advised to take higher doses, ranging from 4 to 5 mg daily. It is important to note that there is currently no consensus on the optimal folate dosage [28].

Observational pregnancy registers have not been able to demonstrate any beneficial effects of folate on the risk of MCMs in offspring of women with epilepsy on ASM treatment [4]. However, folate supplementation has been associated with improved neurodevelopmental outcomes [29]. It is important to note that high-dose folate supplementation has also been linked to an increased risk of childhood cancer [30]. However, such findings are not a proven causal relationship and remain controversial [31]. Therefore, the optimal dose and timing for folate supplementation in women on ASM treatment have yet to be established.

3.10. Outcomes in different populations

Most large-scale cohort studies on pregnancy outcomes in women with epilepsy have been carried out in Europe, North America and Australia [2–4,17,18]. It is unclear whether the results obtained from these studies are applicable to a broader population, including large parts of Asia and Africa. In Asian countries, similar registries are usually led by a single doctor or research team with relatively limited resources, which could be potential barriers for large-scale cohort studies.

4. How can we close the knowledge Gaps?

Due to obvious ethical reasons, many of the unknowns regarding epilepsy and pregnancy cannot be resolved through randomized controlled trials. Therefore, we are limited to observational studies, which come with inherent risks of confounding. This highlights the need for large cohorts to enable adjustments to control for confounders. A major issue with many current cohort studies, such as the epilepsy and pregnancy registries, is that only a fraction of ASM exposed pregnancies is enrolled [2–4]. As a result, it is essential to find ways to increase enrollment in existing observational studies. Large countries in Asia, such as China, present an opportunity to accelerate recruitment and shorten the time to obtain answers to important unsolved questions. One possibility would be to establish new prospective observational studies similar to those operating in Europe, Australia, and North America. However, it would likely be more practical for these countries to join already established pregnancy registries and take advantage of the experience that has been gained.

Some important issues, such as the risks and benefits of different doses of folate supplementation, may be challenging to resolve through observational studies alone [29,30]. To address these questions, randomized controlled trials comparing different doses in large populations of women with epilepsy would be necessary. Implementing such trials could potentially be feasible in large countries like China.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Meadow SR. Anticonvulsant drugs and congenital abnormalities. Lancet 1968;2 (7581):1296.
[2] Hernández-Díaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, et al. North American AED Pregnancy Registry. Comparative safety of antiepileptic drugs during pregnancy. Neurology 2012 May 22;78(21):1692–9.
[3] Campbell E, Kennedy F, Russell A, Smithson WH, Parsons L, Morrison PJ, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. J Neurol Neurosurg Psychiatry 2014 Sep;85(9):1029–34.
[4] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol 2018;17(6):530–8.
[5] Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol 2013;12(3):244–52.
[6] Bjørk MH, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. JAMA Neurol 2022;79(7):672–81.
[7] Cohen JM, Alvestad S, Cesta CE, Bjørk MH, Leinonen MK, Nørgaard M, et al. Comparative Safety of Antiseizure Medication Monotherapy for Major Malformations. Ann Neurol 2023;93(3):551–62.
[8] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10(7):609–17.
[9] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Declining malformation rates with changed antiepileptic drug prescribing: An observational study. Neurology 2019;93(9):e831–40.
[10] Viale L, Allotey J, Cheong-See F, Arroyo-Manzano D, Mccorry D, Bagary M, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 2015 Nov 7;386(10006):1845–52.
[11] Mazzone PP, Hogg KM, Weir CJ, Stephen J, Bhattacharya S, Chin RFM. Comparison of Perinatal Outcomes for Women With and Without Epilepsy: A Systematic Review and Meta-analysis. JAMA Neurol 2023 May 1;80(5):484–94.
[12] Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia 2014;55(7):e72–4.

[13] Pennell PB, Karanam A, Meador KJ, Gerard E, Kalayjian L, Penovich P, et al. Antiseizure Medication Concentrations During Pregnancy: Results From the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Study. JAMA Neurol 2022;79(4):370–9.
[14] Tomson T, Battino D, Bromley R, Kochen S, Meador KJ, Pennell PB, et al. Breastfeeding while on treatment with antiseizure medications: a systematic review from the ILAE Women Task Force. Epileptic Disord 2022;24(6):1020–32.
[15] Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. JAMA Pediatr 2014 Aug;168(8):729–36.
[16] 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 Nov;70(11):1367–74.
[17] Veroniki AA, Cogo E, Rios P, Straus SE, Finkelstein Y, Kealey R, et al. Comparative safety of antiepileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med 2017 May 5;15(1):95.
[18] Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 2016 Nov;7;11(11):CD010224.
[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(3):579–88.
[20] Hernández-Díaz S, McElrath TF, Pennell PB, Hauser WA, Yerby M, Holmes LB. North American Antiepileptic Drug Pregnancy Registry. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. Ann Neurol 2017 Sep;82(3):457–65.
[21] Holmes LB, Mittendorf R, Shen A, Smith CR, Hernandez-Diaz S. Fetal effects of anticonvulsant polytherapies: different risks from different drug combinations. Arch Neurol 2011;68(10):1275–81.
[22] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology 2015;85(10):866–72.
[23] Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. J Am Med Assoc 2013;309(16):1696–703.
[24] Paulzen M, Stingl JC, Augustin M, Saßmannshausen H, Franz C, Gründer G, et al. Comprehensive Measurements of Intrauterine and Postnatal Exposure to Lamotrigine. Clin Pharmacokinet 2019 Apr;58(4):535–43.
[25] Shawahna R, Zaid L. Concentrations of antiseizure medications in breast milk of lactating women with epilepsy: A systematic review with qualitative synthesis. Seizure 2022 May;98:57–70.
[26] Dreier JW, Bjørk MH, Alvestad S, Gissler M, Igland J, Leinonen MK, et al. Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders. JAMA Neurol 2023.
[27] Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. JAMA Pediatr 2014;168(8):729–36.
[28] Tomson T, Battino D, Bromley R, Kochen S, Meador K, Pennell P, 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(6):497–517.
[29] Meador KJ, Pennell PB, May RC, Brown CA, Baker G, Bromley R, et al. Effects of periconceptional folate on cognition in children of women with epilepsy: NEAD study. Neurology 2020;94(7):e729–40.
[30] Vegrim HM, Dreier JW, Alvestad S, Gilhus NE, Gissler M, Igland J, et al. Cancer Risk in Children of Mothers With Epilepsy and High-Dose Folic Acid Use During Pregnancy. JAMA Neurol 2022;79(11):1130–8.
[31] Bjørk MH, Tomson T, Dreier JW, Alvestad S, Gilhus NE, Gissler M, et al. High-dose folic acid and cancer risk; unjustified concerns by von Wrede and colleagues regarding our paper. Epilepsia 2023 Sep;64(9):2244–8.