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EXECUTIVE SUMMARY

Management of epilepsy in pregnancy: A report from the International League Against Epilepsy Task Force on Women and Pregnancy

Torbjörn Tomson[1,2] | **Dina Battino**[3] | **Rebecca Bromley**[4,5] | **Silvia Kochen**[6] | **Kimford Meador**[7] | **Page Pennell**[8] | **Sanjeev V. Thomas**[9]

[1]Department of Clinical Neuroscience, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

[2]Department of Neurology, Karolinska University Hospital, Stockholm, Sweden

[3]Epilepsy Center, Department of Neurophysiology and Experimental Epileptology, Fondazione IRCCS Istituto Neurologico CARLO BESTA, Milan, Italy

[4]Division of Evolution and Genomic Science, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK

[5]Royal Manchester Children's Hospital, Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Central Manchester University, Manchester, UK

[6]Epilepsy Center, ENyS CONICET, Hosp. El Cruce, Hosp. R. Mejía, Univ Buenos Aires, Buenos Aires, Argentina

[7]Department of Neurology & Neurological Sciences, Stanford University, Palo Alto, CA, USA

[8]Divisions of Epilepsy and Women's Health, Department of Neurology, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA

[9]Department of Neurology, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala, India

Correspondence: Torbjörn Tomson, Department of Clinical Neuroscience, Karolinska Institutet, Department of Neurology, Karolinska University Hospital, SE 171 76 Stockholm, Sweden.
Email: torbjorn.tomson@sll.se

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1 | EXECUTIVE SUMMARY

The risks associated with use of antiepileptic drugs (AEDs) during pregnancy are a major concern for all women with epilepsy who are of childbearing potential. These risks need to be balanced against fetal and maternal risks from uncontrolled seizures. This report from the International League Against Epilepsy Task Force on Women and Pregnancy aims to provide a summary of relevant data on these risks as a basis for expert opinion recommendations for the management of epilepsy in pregnancy.[1] The report first reviews data on maternal and fetal risks with seizures as well as teratogenic risks with antiepileptic drug exposure, including effects on intrauterine growth, major congenital malformations, and developmental and behavioral outcomes. The impact of pregnancy on seizure control and on the pharmacokinetics of AEDs is also discussed.

It is concluded that tonic-clonic seizures (of focal or generalized onset) may be associated with risks to the fetus as well as to pregnant woman. Other seizures are probably less harmful, but may be associated with injury, intrauterine growth retardation, and premature delivery.

Most women with epilepsy maintain their seizure control during pregnancy. Prepregnancy seizure control is the most important predictor of seizure control during pregnancy. Nonadherence to AED medication and alterations in AED clearance are major causes of break-through seizures.

Pregnancy can have a major impact on the pharmacokinetics of AEDs. The most marked declines in serum

concentrations during pregnancy are seen with lamotrigine, levetiracetam, and oxcarbazepine, but also phenobarbital, phenytoin, topiramate, and zonisamide undergo clinically relevant increase in elimination. A decline in serum concentration by >35% from prepregnancy optimal concentration is associated with increased risk of deterioration in seizure control. The extent to which pregnancy affects AED blood levels varies between individual women and is best controlled by blood level sampling.

Fetal risks induced by exposure to certain AEDs include intrauterine growth restrictions, major congenital malformation (MCM), negative impact on the offspring's cognition, and increased risk of neurodevelopmental disorders.

It is concluded that the effect on intrauterine growth varies between different AEDs and appears to be most pronounced with topiramate.

Valproate is associated with the highest risk of inducing MCMs, phenobarbital and topiramate with intermediate risks to specific organs, whereas lamotrigine and levetiracetam are associated with the lowest risks. The risk of MCMs is dose-dependent for valproate and probably also for other AEDs such as carbamazepine, phenobarbital, and lamotrigine.

In polytherapy, the types of AEDs included are at least as important for the risk of MCM as the number of drugs.

Exposure in the womb to valproate carries a significant dose-dependent risk to child cognition and neurodevelopmental disorders (eg, autism spectrum disorder). Carbamazepine does not appear to be a major neurobehavioral teratogen. Current data suggest that lamotrigine does not pose a substantial risk to neurodevelopmental outcomes. There are limited data suggesting that levetiracetam and topiramate have low risks for neurodevelopmental problems, but additional information is clearly needed. Data for all other AEDs are lacking in terms of later child cognition.

The second part of this report includes recommendations for the management before and during pregnancy. The recommendations should be considered as based on expert opinion rather than being evidence-based guidelines. This approach was taken because of limitations in the present evidence base, which leave clinicians and their patients without adequate information.

A major challenge in the provision of adequate preconception counseling is unplanned pregnancies. The importance of planning the pregnancy should therefore be brought up regularly in every routine consultation with women with epilepsy that are of childbearing potential. This is the time to reconsider the indication for and the choice of AED treatment. If a change in medication is considered, it should be completed early enough to allow sufficient time to assess the effectiveness of the new regimen before conception. The objective of the treatment review and possible revision is to establish before conception the lowest effective dose of the appropriate AED for the individual woman and to document the associated drug serum concentration, where such facilities are available.

It is also important that adequate folate supplementation is initiated already in the preconception stage. Evidence for the best periconceptional dose of folate in women with epilepsy taking AEDs remains inadequate. Recommendations vary from 0.4 to 4-5 mg/d. Given the incidence of unplanned pregnancies, women of childbearing potential taking AEDs should be on at least 0.4 mg/d of folate.

Once pregnancy occurs, counseling to the patient should reinforce the need for AEDs, and that any potential AED risk to the fetus will be balanced against the risk of increased seizures to both the mother and the developing fetus. If the woman is on an AED that undergoes substantial clearance changes, drug level monitoring is recommended. The individualized target concentration should be reassessed and maintained during pregnancy with blood levels throughout pregnancy.

If antiepileptic blood levels are not available, it is reasonable to consider an increase in dose after the first trimester, at least in women whose epilepsy includes focal to bilateral or generalized tonic-clonic seizures, who have been sensitive to changes in drug levels before pregnancy, and who have entered pregnancy on the lowest effective dose of their medication, AND provided that they are treated with AEDs known to be subject to marked changes in clearance (lamotrigine, levetiracetam, and oxcarbazepine).

In settings where prenatal testing is available and acceptable, relevant tests should be discussed and offered to the woman. If there is a concern for intrauterine growth retardation, then serial ultrasounds may be performed.

The third trimester is a critical time to coordinate recommendations for labor and delivery and early postpartum care between the neurologist and obstetrician. The diagnosis of epilepsy in itself is not an indication for a cesarean section. Vaginal deliveries are the norm.

If AED dosing has been increased during pregnancy, the rate of taper of the drug(s) back to prepregnancy dose or slightly above depends mainly on the primary route of elimination for each individual AED.

Given the known benefits to mother and child of breastfeeding, and studies showing no adverse effects of breastfeeding when taking AEDs, breastfeeding is encouraged.

2 | CONCLUSIONS

The challenge in the management of epilepsy during pregnancy is to balance the fetal and maternal risks associated with seizures against the teratogenic risks with exposure to AEDs in utero. Addressing issues related to pregnancy should begin well before conception in order to maximize pregnancy outcomes. It is clear that AEDs differ in their teratogenic

potential. Valproate is associated with the greatest risks for malformations as well as for adverse cognitive and behavioral outcomes and should, whenever possible, be avoided in the treatment of patients who can become pregnant. Lamotrigine and levetiracetam are associated with the lowest risks for malformations, but data on neurodevelopment for levetiracetam are based on a small sample and evidence on the effects of prenatal exposure on the neurodevelopment is lacking or insufficient for other AEDs. Teratogenic risks should be considered early at the time of initiation of treatment in young female patients. Prepregnancy counseling is essential to ensure that the woman conceives while on folate supplementation and the most appropriate AED treatment with the least risk to the woman and her baby. Once pregnancy is established, close monitoring is warranted and ideally in collaboration between epilepsy care and obstetric care. It should finally be emphasized that the most women with epilepsy will have uneventful pregnancies and give birth to normal children. The aim of the recommendations in this review is to further facilitate such positive pregnancy outcomes.

CONFLICT OF INTERESTS

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ORCID

Torbjörn Tomson https://orcid.org/0000-0003-0554-5352
Sanjeev V. Thomas https://orcid.org/0000-0001-5307-3551

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