Antiepileptic drugs in pregnancy and hemorrhagic disease of the newborn

An update

Aleksey Kazmin MD **Renee C. Wong** MB BS **Mathew Sermer** MD FRCSC **Gideon Koren** MD FRCPC FACMT

ABSTRACT

QUESTION What is the current evidence regarding the association between hemorrhagic disease of the newborn and maternal use of hepatic enzyme-inducing antiepileptic drugs (eg, carbamazepine, phenobarbitone, topiramate)?

ANSWER Women with epilepsy who take enzyme-inducing antiepileptic drugs should be advised that there is no adequate evidence to support or refute taking vitamin K in late pregnancy to prevent bleeding complications in a newborn.

RÉSUMÉ

QUESTION Quelles sont les données scientifiques concernant l'association entre la maladie hémorragique du nouveau-né et l'utilisation par la mère de médicaments antiépileptiques déclenchant la production d'enzymes hépatiques (p. ex. carbamazépine, phénobarbitone, topiramate)?

RÉPONSE Il faudrait conseiller aux femmes atteintes d'épilepsie qui prennent des médicaments antiépileptiques induisant la production d'enzymes qu'il n'y a pas de données factuelles suffisantes pour corroborer ou réfuter le fait que la vitamine K prise en fin de grossesse prévienne les complications hémorragiques chez le nouveau-né.

While evidence of the teratogenicity of antiepileptic drugs (AEDs) has been fairly consistent, whether there is an increased risk of hemorrhagic disease of the newborn secondary to maternal use of AEDs is still unclear.

Newborn infants are vulnerable to hemorrhagic disorders owing to limited transplacental transfer of vitamin K and limited fetal storage of vitamin K.[1,2] The current frequency of vitamin K deficiency bleeding in the first week of life in infants not receiving vitamin K prophylaxis has been estimated at 0.01% to 0.44%.[3,4] However, the clinical presentation of bleeding disorders in newborns is often severe, with a mortality rate of 20%, intracranial hemorrhage occurring in 50%, and common persistent neurologic impairment. Incidence of bleeding complications in fully breastfed infants who did not receive vitamin K at birth is between 1 in 15 000 and 1 in 20 000 births.[5]

To prevent bleeding complications, vitamin K prophylaxis shortly after delivery was widely adopted in 1961 for all newborns. However, it has been acknowledged that "vitamin K analogues administered to the mother may frequently be ineffective in preventing the coagulation abnormalities of the infant."[6]

Studies

In the 1970s and early 1980s, several studies described a possible association between maternal use of AEDs and hemorrhagic disease of newborns.[7,8] These small studies suggested that the use of enzyme-inducing AEDs (eg, carbamazepine, phenobarbitone, topiramate) might induce fetal hepatic enzymes, resulting in vitamin K deficiency, and thus increase the risk of neonatal bleeding.[9] In 1982, a small study recommended routine vitamin K prophylaxis for all epileptic mothers near term.[8] A daily oral dose of 20 mg of vitamin K has been suggested but has not been proven to be effective.

After summarizing all available data, the American Academy of Neurology concluded in 1998 that "the prenatal administration of oral vitamin K to pregnant WWE [women with epilepsy] taking AEDs to prevent early first 24 hours of life hemorrhagic disease of the newborn is theoretically useful."[10] Prenatal vitamin K supplementation of 10 mg per day from the 36th week of gestation until delivery was suggested. Although this recommended dose of oral vitamin K was not supported by any specific study, it has been a widely accepted recommendation.

In 2002, Kaaja et al conducted the first evidence-based study of enzyme-inducing AEDs in pregnancy, analyzing 667 offspring of 452 women with epilepsy taking enzyme-inducing AEDs.[11] None of the mothers received vitamin K during pregnancy, but all infants

received 1 mg of vitamin K_1 intramuscularly at birth. The control subjects were 1324 nonepileptic mothers (1334 neonates) matched for maternal age, parity, number of fetuses, and delivery date. Bleeding complications were observed in 5 (0.7%) of the offspring exposed to maternal enzyme-inducing AEDs and in 5 (0.4%) control subjects ($P=0.3$). After logistic regression, bleeding disorders were associated with birth at less than 32 weeks of gestation (adjusted odds ratio [AOR] 13, 95% confidence interval [CI] 2.7 to 64) and maternal alcohol abuse (AOR 17, 95% CI 1.8 to 162) but not with exposure to enzyme-inducing AEDs (AOR 1.1, 95% CI 0.3 to 4.6). This study did not support the hypothesis that maternal enzyme-inducing AEDs increased the risk of bleeding in the offspring.

In 2004, Choulika et al conducted a retrospective cohort study, analyzing 169 infants exposed to AEDs and 77 unexposed control infants.[12] Only one woman had received vitamin K supplementation in the last weeks of pregnancy. Despite the lack of vitamin K supplementation in all but one woman with epilepsy at the end of the pregnancy, this study did not confirm bleeding tendencies in the infants exposed to anticonvulsant drugs: 12 (7.1%) infants in the group exposed to anticonvulsant drugs and 10 (12.9%) infants in the unexposed control group.

Conclusion

The American Academy of Neurology updated its recommendations in April 2009.[13] Harden et al evaluated "the available evidence based on a structured literature review and classification of relevant articles published between 1985 and October 2007." In their conclusion, they stated "there is inadequate evidence to determine if the newborns of WWE taking AEDs have a substantially increased risk of hemorrhagic complications."[13] Additionally, there is no adequate evidence that oral prenatal vitamin K supplementation in women with epilepsy diminished neonatal bleeding complications. In the clinical context, this analysis strengthens the practice of giving vitamin K at delivery to newborns exposed to enzyme-inducing AEDs in utero as is the routine practice for all newborns.

Competing interests
None declared

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Dr Wong** is a Fellow and **Dr Sermer** is Professor in the Department of Obstetrics and Gynaecology at the University of Toronto. **Dr Kazmin** is a member and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology in the Department of Medicine at the University of Western Ontario in London.

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