



# Motherisk Update

## Does vitamin K prophylaxis prevent bleeding in neonates exposed to enzyme-inducing antiepileptic drugs in utero?

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### ABSTRACT

**QUESTION** One of my epileptic patients takes carbamazepine. She is 36 weeks pregnant and has asked me whether she should start vitamin K to prevent neonatal bleeding. Does current evidence support this practice?

**ANSWER** Recent evidence does not support the notion that newborns of women treated with enzyme-inducing anticonvulsant drugs are at increased risk of hemorrhagic disease. Antenatal vitamin K can be prescribed on an individualized basis in certain circumstances, such as imminent premature delivery.

### RÉSUMÉ

**QUESTION** L'une de mes patientes qui est épileptique prend de la carbamazépine. Elle en est à sa 36<sup>e</sup> semaine de grossesse et m'a demandé si elle devrait commencer à prendre de la vitamine K pour prévenir une hémorragie néonatale. Existe-t-il actuellement des données scientifiques justifiant une telle pratique?

**RÉPONSE** Les données scientifiques récentes ne confirment pas la notion que les nouveau-nés de femmes traitées avec des médicaments anticonvulsivants par induction enzymatique courent un risque accru de troubles hémorragiques. On peut prescrire de la vitamine K sur une base individualisée, dans certaines circonstances, comme un accouchement prématuré imminent.

Epilepsy is the most common major neurologic complication of pregnancy. The prevalence of epilepsy in the general population is between 0.6% and 1%; about 0.5% of all pregnant women have epilepsy.<sup>1</sup> Several problems related to both mothers and babies should be considered. One concern is neonatal bleeding secondary to in utero exposure to enzyme-inducing antiepileptic drugs (AEDs). Therapy with enzyme-inducing AEDs has been thought to cause vitamin K deficiency in neonates born to women with epilepsy. More than 40 reports associate neonatal bleeding with maternal anticonvulsant therapy.<sup>2-8</sup> The mechanism by which AEDs could cause bleeding in newborns involves alterations in vitamin K metabolism.<sup>2,9</sup>


Enzyme-inducing AEDs, such as phenobarbital, phenytoin, and carbamazepine, cross the placenta and induce hepatic microsomal enzymes in the fetal liver. These enzymes might induce degradation of vitamin K. Prenatal administration of oral vitamin K to pregnant women with epilepsy taking AEDs is aimed at preventing hemorrhagic disease in newborns during their first day of life. Recommendations to give epileptic mothers vitamin K during the last month of pregnancy have been based on case reports suggesting the offspring of mothers using enzyme-inducing AEDs have vitamin K deficiency.<sup>2,9-11</sup> Administration of vitamin K to mothers

is in addition to the prophylactic vitamin K given to all infants.<sup>12,13</sup> An estimated 24% to 40% of women with epilepsy receive vitamin K prophylaxis during the last month of pregnancy.<sup>14,15</sup>

Evidence-based reports do not support this practice, however. Kaaja et al<sup>16</sup> followed 667 offspring of 452 women using enzyme-inducing AEDs (mostly carbamazepine). Among the 667 fetuses, 528 (78.7%) were exposed to monotherapy, and 142 (21.3%) were exposed to polytherapy. Eighty-five fetuses (12.7%) were also exposed to one or more drugs that were not enzyme inducers (valproate, clonazepam, diazepam, or clobazam). Five infants in this study developed intracranial hemorrhage; 3 of the 5 were born before 34 weeks' gestation. Another 2 infants had complications known to predispose them to intracranial bleeding, such as intrauterine asphyxia, sepsis, fetal alcohol syndrome, or placental disease. Control subjects were 1324 nonepileptic pregnant women with 1334 neonates matched for maternal age, parity, number of fetuses, and delivery date. None of these mothers received vitamin K during pregnancy. Interestingly, there were also only 5 neonates with bleeding complications among the offspring of these control subjects.

Although this cohort study does not support routine use of antenatal vitamin K, prophylaxis might be worth

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considering when premature delivery is imminent in women using AEDs.<sup>17</sup> There is an obvious need for more studies on the risk of bleeding in newborns exposed to enzyme-inducing AEDs, comparing them with unexposed controls. This clinical question highlights the fact that practice guidelines are sometimes not founded on solid evidence. 

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# MOTHE RISK

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