Practice parameter update: management issues for women with epilepsy - focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.

Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society


CRD summary
This review concluded there was some evidence to support active monitoring of anti-epileptic drug levels during pregnancy in women with epilepsy, but that the studies did not provide evidence on whether adoption of a monitoring programme would result in improved seizure control during pregnancy. Limitations and inconsistencies in reporting make it difficult to establish whether the review's conclusions are reliable.

Authors' objectives
To assess the evidence for management issues related to the care of women with epilepsy during pregnancy, including pre-conception folic acid use, prenatal vitamin K use, risk of haemorrhagic disease of the newborn, clinical implications of placental and breast milk transfer of anti-epileptic drugs, risks of breast feeding and change in anti-epileptic drug levels during pregnancy.

Searching
Search details were reported in a related paper (see Other Publications of Related Interest), which stated that MEDLINE, Current Contents and BIOSIS Previews databases were searched from December 1985 to June 2007 for relevant studies, published in any language with an English abstract. Hand searches were conducted up to February 2008. Bibliographies of reviews and meta-analyses were also examined for relevant publications. However, the abstract of the current article indicated that searches were conducted up to October 2007.

Study selection
Studies that investigated the use of anti-epileptic drugs in women with epilepsy were eligible for inclusion in the review. For specific review questions, studies were eligible for inclusion if they measured: pre- and post-conception anti-epileptic drugs levels; the association between pre-conception folic acid supplementation and major congenital malformations in neonates; the risk of haemorrhagic complications in neonates (and association with prenatal vitamin K supplementation); placental transfer and breast milk penetration of maternally ingested anti-epileptic drugs in studies with at least five mother-child/maternal serum-breast milk pairs. For one question, controlled studies that compared the frequency of symptomatic effects in neonates between women with epilepsy and on anti-epileptic drugs and not on anti-epileptic drugs were eligible for inclusion.

All included studies were observational in design, the majority of which were non-controlled prospective cohort studies.

At least two reviewers were involved in the selection of studies for inclusion (the analytical process was reported in a related paper; see Other Publications of Related Interest).

Assessment of study quality
Included studies were classified (from class I to IV) according to pre-specified criteria relating to: study design; representativeness of study sample; comparability at baseline; methods used to minimise confounding and bias; and definition of outcomes.

Four reviewers independently classified the studies with disagreements resolved by discussion and consensus (the analytical process was reported in a related paper, see Other Publications of Related Interest).

Data extraction
Where relevant, absolute risks and odds ratios (ORs) with related 95% confidence intervals (95% CIs) were extracted from the included studies. If not reported, these values were calculated where possible (the analytical process was reported in a related paper, see Other Publications of Related Interest). The reviewers contacted the authors of one study to obtain additional data.

The review authors did not state how many reviewers performed the extraction.

**Methods of synthesis**
The studies were combined in a narrative synthesis, grouped by study question. Only studies rated class III or higher appear to have been included in the synthesis.

**Results of the review**
The authors did not state how many studies were identified by the searches or were included in the review. Details of 41 different studies were presented in the data extraction tables (in supplementary online appendices).

Pre-conception folic acid supplementation was possibly effective in preventing major congenital malformations in neonates of women with epilepsy taking anti-epileptic drugs (two class III studies). There was inadequate evidence to determine if such neonates were at increased risk of haemorrhagic complications (one class II study).

Primidone and levetiracetam probably transferred into breast milk in clinically important amounts; valproate, phenobarbital, phenytoin and carbamazepine probably did not (one class I study and a supporting class II study, or two class II studies).

Pregnancy probably caused an increase in the clearance and a decrease in the concentration of lamotrigine (one class I study and a supporting class II study, or two class II studies), phenytoin (one class I study) and to a lesser extent carbamazepine (one class I study), as well as the decrease in level of active oxcarbazepine metabolite, monohydroxy derivative (two class III studies).

**Authors' conclusions**
The reviewed studies provided some evidence to support active monitoring of anti-epileptic drugs levels during pregnancy, particularly for lamotrigine. It seemed reasonable to aim to maintain an anti-epileptic drugs level near the pre-conception level. However, the studies did not provide evidence on whether adoption of an anti-epileptic drugs monitoring programme would result in improved seizure control during pregnancy.

**CRD commentary**
The review question was vaguely defined in terms of the participants, interventions and outcomes of interest. Attempts were made to identify relevant evidence from multiple sources, regardless of language. However, search dates were inconsistent with the cited methods paper. With the exception of data extraction, the authors reported attempts to minimise bias at each stage of the review process.

The validity of studies was broadly assessed using established criteria; this assessment was incorporated into the synthesis. The use of a narrative synthesis appeared appropriate given the apparent heterogeneity of the included studies, although the precise number of studies examined was not entirely clear from the presented text and tables.

Limitations and inconsistencies in reporting make it difficult to establish whether the review's conclusions are reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that the following may be considered: supplementing women with epilepsy with at least 0.4mg of folic acid before they become pregnant; and monitoring of lamotrigine, carbamazepine, phenytoin, levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy.

**Research:** The authors stated that further research is needed on the effects of pre-conception folic acid supplementation on prevention of major congenital malformations, effect of late-pregnancy vitamin K supplementation on the risk of
haemorrhagic disease, and the effect of anti-epileptic drugs use during pregnancy on long-term outcomes in exposed neonates. They added that further data is required in order to determine the management of anti-epileptic drugs dosing in the postpartum period.

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**Other publications of related interest**


**Indexing Status**
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**MeSH**
Anticonvulsants /adverse effects /pharmacokinetics /therapeutic use; Breast Feeding; Congenital Abnormalities /epidemiology /prevention & control; Epilepsy /drug therapy /epidemiology /physiopathology; Female; Folic Acid /administration & dosage; Humans; Infant, Newborn; Milk, Human /metabolism; Placenta /metabolism; Pregnancy; Pregnancy Complications /drug therapy; Risk; Vitamin K /administration & dosage; Vitamin K Deficiency Bleeding /epidemiology /etiology /prevention & control

**AccessionNumber**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.