Q11: 11a). In women with epilepsy, should antiepileptic therapy be prescribed as monotherapy or polytherapy to decrease the risk of fetal malformations?

11b). Does the use of folic acid preconceptually decrease the risk of foetal malformations in women with epilepsy?

11c). Do phenytoin, phenobarbital, valproic acid or carbamazepine enter breast milk in quantities which are clinically significant to the baby?

Background

Women with epilepsy become pregnant, and most have uneventful pregnancies and healthy babies. It is, however, clear that women with epilepsy are at increased risk of having babies with congenital malformations. It has been difficult to clarify the relative contribution of the epilepsy disorder itself, seizure frequency during pregnancy, socio-economic factors, common antiepileptic drugs (AED) in pregnancy in women with epilepsy and the teratogenic effects of AEDs. Several lines of evidence support the latter having a major contribution. These include higher rates of malformations amongst infants born to mothers with treated epilepsy compared to those that are untreated (Kaneko 1988; Rating et al, 1982; Nakane 1980). The need for seizure control has to be balanced against these risks.

In the general population, use of folic acid preconceptually has been shown to reduce the risk of neural tube and other congenital defects in the offspring. The dose of folic acid recommended is higher in women with a past or family history of a child with a neural tube defect, and this higher dose has been extrapolated to women with epilepsy who also have increased risk of neural tube defects associated with the use of AEDs. It is not clear whether this will prevent the teratogenetic effects of enzyme-inducing AEDs or neural tube defects associated with valproate.

The decision whether or not to breast-feed has to balance the benefits to mother and child with the risk of toxicity to the infant. It is important to know whether the risks outweigh the benefits.

Population/Intervention (s)/Comparison/Outcomes (PICO)

Population:	women with epilepsy who may become pregnant.
	women with epilepsy on AED wishing to breast feed.
Interventions:	use of AEDs as monotherapy or polytherapy during pregnancy
	use of phenobarbital, phenytoin, valproate or carbamazepine during pregnancy
	use of folic acid preconceptually and during early pregnancy
	breast feeding while taking phenobarbital, phenytoin, valproate or carbamazepine
Comparison:	pregnant women with epilepsy taking no AEDs.
	pregnant women without epilepsy
Outcomes:	congenital malformations in the infant
	clinically important amounts of AEDs secreted in breast milk

List of the systematic reviews identified by the search process

No systematic review was found which compared the risk of congenital malformations in the offspring of women with epilepsy taking AEDs compared with those not taking AEDs. A Cochrane review (Adab et al, 2004) has reported on neurodevelopmental outcomes in children exposed to AEDs in utero, but has not reported on malformations. Another Cochrane review (Winterbottom et al, 2008) aimed to determine the effectiveness of preconceptual counselling for women with epilepsy, but found no studies which met the inclusion criteria.

Meador et al, 2008b performed a systematic review on the incidence of congenital malformations in the offspring of women with epilepsy. They calculated Poisson incidence (with 95% confidence intervals) for various pregnancy outcomes per pregnancy or per birth in women taking various AEDs and also provided Poisson incidence for the same outcomes in women without epilepsy. They did not provide relative risk (RRs) or Odds ratio (ORs) comparing these data, but indicated where the incidence differed from that in women without epilepsy at the $P<0.05$ level.

A systematic review published in 2004 (Fried et al, 2004) compared rates of malformation in women with untreated epilepsy and healthy controls.

A review published in 2009 (Harden et al, 2009) looked at the evidence regarding folic acid and breast milk.

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
I	Use of AEDs as monotherapy or polytherapy during pregnancy, compared with pregnant women without epilepsy.	Congenital malformations in the offspring	Meador et al, 2008b	The only systematic review which provided pooled data.
2	Use of phenobarbital, phenytoin, valproate or carbamazepine during pregnancy, compared with women without epilepsy.	Congenital malformations in the offspring	Meador et al, 2008b	The only systematic review which provided pooled data.
3	Use of folic acid preconceptually and in early pregnancy in women with epilepsy.	Congenital malformations in the offspring	Harden et al, 2009 (NOT GRADED)	No pooled data calculated
4	Breast feeding by women with epilepsy taking phenobarbital, phenytoin, valproate or carbamazepine	Clinically important amount of AEDs secreted in breast milk	Harden et al, 2009 (NOT GRADED)	No pooled data calculated

Narrative description of the studies that went into the analysis (including a study-by-study table if appropriate)

Use of AEDs in pregnancy

Meador et al, 2008b performed a systematic review (to May 2007) on the incidence of congenital malformations in the offspring of women with epilepsy on AEDs. They calculated Poisson incidence (with 95% confidence intervals) for different events per pregnancy and also indicated Poisson incidence for the same outcomes in women without epilepsy. They did not provide RRs or ORs comparing these data, but indicated where the incidence differed from that in women without epilepsy at the P<0.05 level. The data for all congenital malformations were GRADEd – see below.

Use of Folic acid

Harden et al, 2009 considered the evidence relating to women with epilepsy and, amongst other issues, considered preconceptual folic acid, and breast feeding. The methodology (Harden et al, 2009) included a thorough search of five databases for articles published between 1985 and 2005, which was updated until June 2007. The review found 11 articles in all, but only five were rated as high as class III. The five studies are detailed in the study by study table below.

Reference	Design	Sample size and demographics	Comparison methods	Limitations	Results
Betts and Fox, 1999	Prospective cohort observational study of people referred to a pregnancy counselling clinic preconceptually.	N=85.	Compared with group referred from another hospital, already pregnant. N=59.	Comparison group already pregnant, likely to have complicated pregnancies. Many confounders. Counselled group had AEDs rationalized and minimized.	All of counselled groups took folic acid, plus some of comparison group. None of 97 on folic acid had major malformations in the offspring compared with 11/47 not on folic acid.
Kaaja et al, 2003	Prospective cohort of women diagnosed with epilepsy before pregnancy. None had preconceptual folic acid.	N=970	Compared low and normal serum folate levels measured at	Confounders (AEDs). No folic acid preconceptually.	Log regression showed congenital malformations associated with low maternal educational level, carbamazepine, valproate, oxcarbazepine and low folate levels. OR for folate <4.4nmol/L = 5.8 (95%

	All advised to take multivitamins including 0.1 to 0.8mg folate at first antenatal visit (usually 8 to 12 weeks pregnancy).		end of first trimester.		CI 1.3 to 27)
Vajda et al, 2003	Prospective cohort study – Australian epilepsy register	N=334	Internal comparisons	Only some were prospective. Others retrospective. Self-referred. Data unclear.	Valproate – 97 pregnancies – 16 birth defects (10 mothers had taken preconceptual folic acid); No AED-23 pregnancies, 1 birth defect (mother had taken preconceptual folic acid). Data showed "that folate supplementation before conception did not seem to be protective against AED associated birth defects (p=0.8)."
Vajda et al, 2004	Prospective cohort study – same population as Vajda et al, 2003, with 10 months further follow- up (FU)	N=403	Internal comparisons	Same limitations as Vajda et al, 2003.	In 119 pregnancies exposed to valproate, there were 19 birth defects. 65% of those with no birth defect had mothers taking folic acid preconceptually compared with 53% of those with birth defects.
Wyszynski et al, 2005	Prospective cohort observational study – North American AED Pregnancy register.	N=149 on valproate monotherapy. N= 1048 (other AED monotherapy)	Internal and external comparison of major malformations on AED monotherapy	Self-referred. (All prospective)	16 infants (10.7%) with confirmed major malformations among 149 pregnancies exposed to valproate. Mothers of all 16 took either folic acid or vitamins/ multivitamins preconceptually. 30 infants (2.9%) with major malformations among 1048 pregnancies exposed to other AED monotherapy.

GRADE tables

Question 11 a: Use of AEDs in pregnancy

Table 1

Author(s): G Bell T Dua N Huynh
Date: 2009-08-07
Question: Should Antiepileptic drug monotherapy be used in pregnant women with epilepsy?
Settings: Not stated
Bibliography: Meador K et al (2008b). Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Research,* 81:1-13.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Antiepileptic drug monotherapy	control	Relative (95% CI)	Absolute		
Total congenital malformations (Better indicated by lower values)												
59[1]	observational studies	very serious[2]	serious[3]	no serious indirectness	no serious imprecision[4]	none	0	0	-	MD 0 higher (0 to 0 higher)	VERY LOW	CRITICAL

[1] 59 studies included in all the calculations. Article does not state which studies are included in which calculations. 7 treatment arms reporting total malformations in women on AED monotherapy and 9 treatment arms reporting total malformations in women without epilepsy.
[2] Observational studies. May have incomplete follow up.
[3] Most meta-analytic studies were significant for the test of heterogeneity.
[4] No formal comparison supplied, but results are not statistically significant p<0.05 when compared with women without epilepsy. Poisson incidence of total congenital malformations 5.30 (95% CI 3.51 to 7.09) in women on AED monotherapy compared with 3.27 (95% CI 1.37 to 5.17) in women without epilepsy.

Table 2

Author(s): G Bell T Dua N Huynh
Date: 2009-08-07
Question: Should AED polytherapy be used in pregnant women with epilepsy?
Settings: Not stated
Bibliography: Meador K et al (2008b). Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Research,* 81:1-13.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	AED polytherapy	control	Relative (95% CI)	Absolute		
Total congenital malformations												
59[1]	observational studies	very serious[2]	serious[3]	no serious indirectness	no serious imprecision[4]	strong association[5]	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[1] 59 studies included in all the calculations. Article does not state which studies are included in which calculations. Four treatment arms reporting total malformations in women on AED polytherapy and 9 treatment arms reporting total malformations in women without epilepsy.
[2] Observational studies. May have incomplete follow up
[3] Most meta-analytic studies were significant for the test of heterogeneity
[4] No formal comparison supplied, but results are statistically significant p<0.05 when compared with women without epilepsy. Poisson incidence of total congenital malformations 9.84 (95% CI 7.82 to 11.87) in women on AED polytherapy compared with 3.27 (95% CI 1.37 to 5.17) in women without epilepsy.
[5] Differences in poisson incidence significant.

Table 3

Author(s): G Bell T Dua N Huynh
Date: 2009-08-07
Question: Should phenobarbital monotherapy be used in pregnant women with epilepsy?
Settings: not stated
Bibliography: Meador K et al (2008b). Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Research,* 81:1-13.

Quality assessment	Summary of findings			Importance
	No of patients	Effect	Quality	

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbital monotherapy	control	Relative (95% CI)	Absolute		
Total congenital malformations												
59[1]	observational studies	very serious[2]	serious[3]	no serious indirectness	no serious imprecision[4]	none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[1] 59 studies included in all the calculations. Article does not state which studies are included in which calculations. 14 treatment arms reporting total malformations in women on phenobarbital monotherapy and 9 treatment arms reporting total malformations in women without epilepsy.
[2] Observational studies. May have incomplete follow up.
[3] Most meta-analytic studies were significant for the test of heterogeneity.
[4] No formal comparison supplied, but results are not statistically significant p<0.05 when compared with women without epilepsy. Poisson incidence of total congenital malformations 4.91 (95% CI 3.22 to 6.59) in women on phenobarbital monotherapy compared with 3.27 (95% CI 1.37 to 5.17) in women without epilepsy.

Table 4

Author(s): G Bell T Dua N Huynh
Date: 2009-08-20
Question: Should phenytoin monotherapy be used in pregnant women with epilepsy?
Settings: Not stated
Bibliography: Meador K et al (2008b). Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Research,* 81:1-13.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	phenytoin monotherapy	control	Relative (95% CI)	Absolute		
Total congenital malformations												
59[1]	observational studies	very serious[2]	serious[3]	no serious indirectness	no serious imprecision[4]	none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[1] 59 studies included in all the calculations. Article does not state which studies are used in which calculations. 16 treatment arms reporting total malformations in women on phenytoin monotherapy and 9 treatment arms reporting total malformations in women without epilepsy.

[2] Observational studies. May have incomplete follow-up.
[3] Most meta-analytic studies were significant for the test of heterogeneity.
[4] No formal comparison made, but results are not statistically significant when compared with women without epilepsy. Poisson incidence of total congenital malformations 7.36 (95% CI 3.60 to 11.11) in women on phenytoin monotherapy compared with 3.27 (95% CI 1.37 to 5.17) in women without epilepsy.

Table 5

Author(s): G Bell T Dua N Huynh
Date: 2009-08-07
Question: Should carbamazepine monotherapy be used in pregnant women with epilepsy?
Settings: not stated
Bibliography: Meador K et al (2008b). Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Research,* 81:1-13.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Carbamazepine monotherapy	control	Relative (95% CI)	Absolute		
Total congenital malformations												
59[1]	observational studies	very serious[2]	serious[3]	no serious indirectness	no serious imprecision[4]	none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[1] 59 studies included in all the calculations. Article does not state which studies are included in which calculations. 24 treatment arms reporting total malformations in women on carbamazepine monotherapy and 9 treatment arms reporting total malformations in women without epilepsy.
[2] Observational studies. May have incomplete follow up.
[3] Most meta-analytic studies were significant for the test of heterogeneity
[4] No formal comparison supplied, but results are not statistically significant p<0.05 when compared with women without epilepsy. Poisson incidence of total congenital malformations 4.62 (95% CI 3.48 to 5.76) in women on carbamazepine monotherapy compared with 3.27 (95% CI 1.37 to 5.17) in women without epilepsy.

Table 6

Author(s): G Bell T Dua N Huynh
Date: 2009-08-07
Question: Should valproate monotherapy be used in pregnant women with epilepsy?
Settings: not stated
Bibliography: Meador K et al (2008b). Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Research,* 81:1-13.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	valproate monotherapy	control	Relative (95% CI)	Absolute		
Total congenital malformations												
59[1]	observational studies	very serious[2]	serious[3]	no serious indirectness	no serious imprecision[4]	strong association[5]	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)		

[1] 59 studies included in all the calculations. Article does not state which studies are included in which calculations. 19 treatment arms reporting total malformations in women on valproate monotherapy and 9 treatment arms reporting total malformations in women without epilepsy.

[2] Observational studies. May have incomplete follow up

[3] Most meta-analytic studies were significant for the test of heterogeneity

[4] No formal comparison supplied, but results are statistically significant p<0.05 when compared with women without epilepsy. Poisson incidence of total congenital malformations 10.73 (95% CI 8.16 to 13.29) in women on valproate monotherapy compared with 3.27 (95% CI 1.37 to 5.17) in women without epilepsy

[5] Poisson incidence significantly different from women without epilepsy

Additional information that was not GRADEd

AED usage in pregnancy

Meador et al, 2008a in a review based on pregnancy registries, reported that the North American registry found an increased risk of major malformations associated with both valproate (10.7%) and phenobarbital (6.5%) compared to healthy controls. Neither the UK register nor the Australian register appeared to report an increased risk associated with phenobarbital.

The meta-analysis (Fried et al, 2004) comparing malformation rates in women with untreated epilepsy and in women without epilepsy found no significant difference in rates (OR 1.92, 95% CI 0.92 to 4.00). After correction for a probable publication bias, the odds ratio was reduced to 0.99.

Use of folic acid

A study published in 2009 investigated folic acid use by women in the UK pregnancy register (Morrow et al, 2009). The data did not show a protective effect of preconceptual folic acid in women taking AEDs. Paradoxically, those women who received folic acid preconceptually appeared to have a higher risk of a child with a major congenital malformation than those who received folic acid later or not at all.

AEDs and breast feeding

Harden et al, 2009 also reviewed the evidence on breast feeding, particularly whether maternally ingested AEDs cross the placenta, and whether they penetrate into breast milk. One class I study and one class II study provided evidence that primidone and phenobarbital crossed the placenta. Class II studies provided evidence that phenytoin, carbamazepine, levetiracetam, gabapentin, lamotrigine, oxcarbazepine, topiramate and ethosuximide cross the placenta. Studies showed that valproate, phenobarbital, carbamazepine and phenytoin do not significantly penetrate into breast milk. (Primidone, levetiracetam, gabapentin, lamotrigine, topiramate and ethosuximide have significant penetration into breast milk.)

Reference list

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Betts T, Fox C (1999). Proactive pre-conception counselling for women with epilepsy-is it effective? *Seizure,* 8:322-7.

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Harden CL et al (2009). Management issues for women with epilepsy--focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia,* 50:1247-55.

Kaaja E, Kaaja R, Hiilesmaa V (2003). Major malformations in offspring of women with epilepsy. *Neurology,* 60:575-9.

Kaneko S (1988). A rational antiepileptic drug therapy of epileptic women in child bearing age. Japanese Journal of Psychiatry and Neurology, 42:473-82.

Meador KJ et al (2008a). Pregnancy registries in epilepsy: a consensus statement on health outcomes. *Neurology,* 71:1109-17.

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Rating et al (1982). Teratogenic and pharmacokinetic studies of primidone during pregnancy and in the offspring of epileptic women. *Acta Paediatrica Scandinavica,* 71:301-11.

Vajda FJ et al (2003). The Australian registry of anti-epileptic drugs in pregnancy: experience after 30 months. *Journal of Clinical Neuroscience,* 10:543-9.

Vajda FJ et al (2004). Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. *Journal of Clinical Neuroscience,* 11:854-8.

Winterbottom JB et al (2008). Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome. *Cochrane Database Systematic Reviews,* (3):CD006645.

Wyszynski DF et al (2005). Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology,* 64:961-5.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	a. There is no evidence that the use of AEDs in monotherapy regimens in pregnant women with epilepsy may increase the risk of total malformations compared with the risk in women without epilepsy. There was no data available comparing the risk of total malformations in women with epilepsy taking no AEDs. There is some evidence that the use of AED polytherapy in pregnant women with epilepsy increases the risk of total malformations compared with the risk in women without epilepsy. There is no evidence of increased risk in women with untreated epilepsy.

	There is no evidence that the use of carbamazepine monotherapy in pregnant women with epilepsy may increase the risk of total malformations compared with the risk in women without epilepsy. There was no data available comparing the risk of total malformations in women with epilepsy taking no AEDs. The evidence concerning phenobarbital is heterogeneous. The meta-analysis (Meador et al, 2008b) found no increased risk compared with that in women without epilepsy, whilst one pregnancy registry13 reports an increased risk. There is no evidence that the use of phenytoin monotherapy in pregnant women with epilepsy may increase the risk of total malformations compared with the risk in women without epilepsy. There is evidence that the use of valproate monotherapy in pregnant women with epilepsy may increase the risk of total malformations compared with the risk in women without epilepsy. 1b. Two weak observational studies suggest that use of folic acid preconceptually, or higher serum levels of folate at the end of the first trimester, may be associated with a lower risk of congenital malformations. Three other observational studies do not confirm these findings. All studies are observational and subject to confounding. 1c. There is evidence that neither phenobarbital, phenytoin, carbamazepine nor valproate are secreted in clinically significant amounts in breast milk.
Summary of the quality of evidence	All studies on malformations were observational and subject to confounding. Low or very low quality evidence
Balance of benefits versus	In women with epilepsy who are pregnant the need for seizure control has to be balanced against the risk of exposure of the foetus to AEDs. AED

harms	polytherapy has worse outcomes than AED monotherapy, and there is a significantly increased risk of malformations associated with use of valproate. In women with epilepsy, control of seizures should be optimised before pregnancy, ideally with the lowest dose of an AED in monotherapy which controls the seizures. Valproate should be avoided where possible. Most children born to women with epilepsy have no adverse effects. Use of folic acid is recommended for all women with childbearing capacity to reduce the risk of malformations. Data are insufficient to conclude that folic acid reduces the excess risks in women with epilepsy, but there are no data to suggest harm unless the woman has pernicious anaemia. The dose of folic acid to be taken needs to be established. Neither phenobarbital, phenytoin, carbamazepine nor valproate are secreted in clinically significant amounts in breast milk. Breast feeding is beneficial for babies and is recommended.
Values and preferences including any variability and human rights issues	Seizure control on minimum dose of AEDs should be the aim for epilepsy patients. In any part of the world, it is important that as many children as possible are born healthy and without major problems. Breast feeding is important for many reasons in all babies. It is generally recommended that all women contemplating pregnancy should take folic acid preconceptually, provided there is no pernicious anaemia.
Costs and resource use and any other relevant feasibility issues	Preconceptual counselling requires training. For comprehensive management of women with epilepsy, collaboration with health care providers involved in maternal and child health care is required.
Final recommendation(s)	

Women with epilepsy should have seizures controlled as well as possible with the minimum dose of antiepileptic drug taken in monotherapy, wherever possible. Antiepileptic drug polytherapy should be avoided. Valproic acid should be avoided if possible. Strength of recommendation: STRONG Folic acid should routinely be taken by women with epilepsy of child bearing age who are on antiepileptic drugs. Strength of recommendation: STRONG Standard breast feeding recommendations remain appropriate for women with epilepsy on the antiepileptic drugs included in this review (phenobarbital, phenytoin, carbamazepine and valproic acid). Strength of recommendation: STRONG
Any additional remarks Development of global registries and participation and registration of pregnant women with epilepsy should be encouraged.

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic review was found to be relevant without changing the recommendation:

Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, Hopp J, Ting TY, Hauser WA, Thurman D, Kaplan PW, Robinson JN, French JA, Wiebe S, Eilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Shafer PO, Guen CL. Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding. Epilepsia 2009, 50(5):1247–1255, doi: 10.1111/j.1528-1167.2009.02130.x.