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Valproic Acid in Epilepsy
Pregnancy-Related Issues

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Abstract

Valproic acid (sodium valproate) is widely used as a first-line antiepileptic agent. As with many antiepileptic drugs, there are a number of consequences associated with the use of valproic acid in women of child-bearing potential. Most pregnancies have a favourable outcome in women with epilepsy, and these women should not be discouraged from becoming pregnant. Unlike many other antiepileptic drugs, valproic acid has no significant pharmacokinetic interactions with the steroid hormones used in oral contraceptives. During pregnancy, the major risks to mother and child result from loss of seizure control on the one hand, and an elevated risk of major congenital malformations due to antiepileptic drug treatment on the other. In particular, an elevated risk of major congenital malformations associated with valproic acid use has been a consistent finding in studies of patient registries and several large case series. In addition, developmental delay, characterised by low verbal IQ, has also been reported in children exposed to valproic acid *in utero*, although the relative risk is not precisely known. For these reasons, pregnancies in women being treated with valproic acid need to be

planned, and the benefit-risk ratios associated with continuing valproic acid or changing treatment need to be discussed with the patient. When treatment with valproic acid is the most appropriate treatment to achieve optimal seizure control, a number of measures can be implemented to minimise risk to the fetus. These include the use of the lowest possible effective dose of valproic acid in monotherapy (ideally <1000 mg/day), appropriate folic acid supplementation and close antenatal monitoring. Regular counselling is a prerequisite for informed planning of pregnancies and optimisation of the probability of a healthy outcome. Future research on valproic acid and pregnancy should involve risk assessment in large, population-based prospective studies.

Epilepsy is a frequent, severe and potentially incapacitating neurological disorder, with a prevalence of approximately 0.5–1.5%.[1,2] In most cases, epilepsy can be controlled adequately with one of the many available antiepileptic drugs (AEDs). These drugs differ in both the spectrum of epilepsy syndromes in which they are efficacious and in their adverse-effect profiles. The principal drugs used as first-line treatments are valproic acid for generalised epilepsies and carbamazepine for focal epilepsies.[3-5] In particular, valproic acid is often considered the treatment of choice in juvenile myoclonic epilepsy, for which it seems highly effective and for which other equieffective treatment options are limited.[6]

As epilepsy is relatively frequent in young women of childbearing age, the impacts of both epilepsy itself and AED treatment on pregnancy are important issues to consider. Women with epilepsy should not be discouraged from becoming pregnant, as there is a >90% chance of giving birth to a healthy baby in such women, compared with 98% in the general population.[7] For example, data from the UK Epilepsy and Pregnancy Patient Registry (UKEPPR) suggest that the proportion of women with epilepsy having babies with congenital malformations is <5% (4.2% in AED-exposed pregnancies vs 3.5% in non-exposed pregnancies), although this proportion clearly varies according to the individual's AED exposure.[8] However, these pregnancies are often considered as high risk because of the possible loss of seizure control due to endocrine changes or alterations in the disposition of AEDs, and an increased risk of adverse outcomes. There is also a potential risk of long-term adverse effects on postnatal development that remains poorly quantified. Valproic acid has been considered to be more problematic than certain other AEDs in these respects, because of a potential risk of congenital malformations or developmental delay.[9,10] To minimise these risks, women receiving valproic acid who wish to become pregnant need to be fully informed and managed carefully with respect to preparation for pregnancy, medication use and monitoring.

It should be noted that valproic acid is used in the treatment of other conditions, particularly mood disorders. There is no reason to suppose that the issues raised in this review of valproic acid treatment in women with epilepsy should be any different to those in women receiving valproic acid for other indications, although the consequences for care may differ. However, this review focuses specifically on epilepsy, as the vast majority of the available data on the impact of valproic acid treatment on pregnancy concerns this indication. This article reviews the available data on valproic acid in pregnancy in order to identify the real risks to women with epilepsy who are receiving valproic acid and who wish to become pregnant and to suggest a strategy for risk minimization in these cases.

1. Antiepileptic Drugs and Contraception

Many AEDs have significant pharmacokinetic interactions with the steroid hormones used in oral contraceptive preparations. This can have clinically important consequences, including contraceptive failure and loss of seizure control. These interactions are principally due to induction of the cytochrome P450 (CYP) 3A4 isoenzyme, which is responsible for the metabolism of estrogens and

progestins, by AEDs such as carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone and topiramate.[11-13] This results in increased metabolism of exogenous estrogens and progestins, with a consequent reduction in plasma concentrations that may cause contraceptive failure. Contraceptive failure is sometimes manifested by breakthrough bleeding but is often clinically silent, resulting in a risk of unwanted pregnancies. In this respect, specific warnings have recently been added to the official prescribing information for lamotrigine. In addition, and perhaps more importantly, oral contraceptives reduce the concentration of lamotrigine to a clinically important extent, with the possibility of impaired seizure control when oral contraceptive therapy is initiated.[13-15]

Because of these potentially important interactions, contraception needs to be adapted in accordance with the AED treatment that the patient is receiving, either by increasing the dosage of estrogen, using a transdermal formulation or by switching to an alternative form of contraception. An alternative approach would be to switch epilepsy treatment to an AED that does not induce CYP3A4. However, such considerations are not always made, as revealed by a large primary care patient registry survey of women with epilepsy in the UK, which found that contraception was not adapted for concomitant AED treatment in over half of the patients, thus putting them at risk for contraceptive failure and unwanted pregnancy.[16] A survey of US neurologists and obstetricians showed that only 45% of the neurologists and none of the obstetricians were aware of the interactions between commonly used AEDs and oral contraceptives, despite the fact that they had often been confronted with contraceptive failure in patients taking AEDs.[17]

Valproic acid does not induce CYP3A4 and thus does not interact with oral contraceptives.[18] It is one of the few extensively used drug therapies for epilepsy that does not interact with oral contraceptives.

2. Valproic Acid and Major Congenital Malformations

Although the vast majority of women with epilepsy have normal, healthy babies, a number of studies have identified an increased risk of congenital malformations. This risk is generally considered to be associated principally with exposure to AEDs, including valproic acid, rather than with epilepsy itself; the possible association of epilepsy with an elevated risk of malformations remains very controversial.

The idea that the use of AEDs may be associated with congenital malformations originally arose from a number of case reports dating back to the early 1970s. These reports frequently concerned phenytoin, more widely prescribed then than it is today, and led to the notion of the fetal hydantoin syndrome.[19] This syndrome typically comprises facial dysmorphism with wide-spaced eyes, deformed fingers and fingernails, and retarded development, although more severe malformations such as hip dysplasias, facial clefts and cardiac abnormalities are occasionally seen. However, these reports were largely anecdotal and, in the absence of controlled, large-scale studies, the true incidence of the fetal hydantoin syndrome, and the relative risk of this with phenytoin use compared with the use of other AEDs, could not be estimated until recently. During the intervening period, the use of phenytoin has declined following the introduction of other better tolerated AEDs.

2.1 Epilepsy and Pregnancy Outcomes

Some studies have suggested that maternal seizures, particularly during the first trimester, increase the risk of minor craniofacial malformations, possibly due to reduced placental blood flow.[20,21] However, these results have not been confirmed by larger, more recent studies.[22] Holmes et al.[23] reported malformation rates were not higher in 98 women with untreated epilepsy compared with 508 women without epilepsy, whereas rates were significantly higher in 316 women with epilepsy who were receiving AEDs. The same conclusion was drawn from another study in 1411 children born to women with epilepsy who were treated during the first trimester and 2000 control children.[24] Similarly, data from the UKEPPR did not reveal an elevated major congenital malformation rate in children born to untreated women with epilepsy with respect to the general population.[8] A recent meta-analysis of estimates of malformation rates in untreated women with epilepsy concluded that there is no specific

teratogenic risk attributable to epilepsy *per se*.[25] Overall, the available evidence is not in favour of a systematic relationship between non-treated epilepsy and congenital malformations. If seizures do contribute to an increased risk of congenital malformations, albeit a minor increase, seizure type is likely to be a critical determinant, with the malformation risk being highest among those with generalised tonic clonic seizures and lower for patients who experience focal, absence or myoclonic seizures.

2.2 Antiepileptic Drugs and Pregnancy Outcomes

With respect to AED exposure, teratogenic effects have been suspected from case reports and small case series for many years. Neural tube defects are considered to be of particular concern in infants exposed to valproic acid, and to a lesser extent, carbamazepine, the two most frequently used AEDs. More recently, several larger studies have aimed to include sufficient patients to quantitate this risk and to determine the relative risks associated with different AEDs.[26,27] The principal studies are briefly reviewed in table I and the, estimated therein, relative risks of major malformations (presented as odds ratios [ORs] with respect to carbamazepine) associated with the most extensively studied AEDs that are used as monotherapy are presented in figure 1. An elevated risk of major congenital malformations associated with valproic acid exposure has been a consistent finding in these studies, even though the relative risk may not be always significantly different from the reference group because of the relatively low number of cases involved.

There are a number of limitations to the conclusions that can be drawn from these studies. First, they have principally evaluated phenobarbital, phenytoin, carbamazepine and valproic acid, the principal AEDs used as monotherapy, and there is consequently little information available on the third-generation AEDs, such as lamotrigine, oxcarbazepine, gabapentin, topiramate, tiagabine, vigabatrin and levetiracetam. This is primarily due to the fact that these drugs, with the exception of lamotrigine, are not widely used, if at all, as monotherapy and secondly, to their relatively recent introduction in relation to the time base of enrolment of these studies, which in some cases began over 20 years ago. Another consequence of the relatively dated populations included in these studies is that they do not reflect the potential teratogenic impact of more recent extended-release formulations of certain AEDs, such as carbamazepine and valproic acid, which are now widely prescribed.[31] Additionally, the sample sizes in these studies are relatively small, which compromises the demonstration of significant differences between the malformation rates associated with the individual AEDs. Importantly, the various studies have not provided consistent information on either the absolute malformation rates or the relative risks associated with the individual AEDs, which prevents the drawing of conclusions with any certitude. It is possible that some of the identified variability in the malformation rates is attributable to differences between countries and over time, to differences in the doses of AEDs prescribed and the indications for which they are used, thus introducing important variation in exposure. Finally, the studies do not take into account independent determinants of congenital malformations that may be unevenly distributed between the studies and treatment groups. These include epilepsy-related variables; particularly epileptic syndrome, seizure type and severity; and epilepsy-independent variables, such as socioeconomic status, general health and comorbidities.

2.2.1 Retrospective and Prospective Case Series

The first large-scale evaluation of the malformation rates associated with AED exposure *in utero* was a pooled analysis of five individual prospective studies performed in three European countries (Finland, Germany and The Netherlands).[28] The total sample size was 1221 children exposed to AEDs from 1972 to 1990, which gives the analysis substantially more power than the original source studies. Crude major congenital malformation rates varied from 6% for phenytoin monotherapy to 10% for phenobarbital monotherapy, with much higher rates being observed with polytherapy. In one of the source studies, a group of 158 unexposed infants born to women without epilepsy were also studied, allowing an estimation of relative risks compared with unexposed infants. Elevated relative risks were observed for carbamazepine (OR: 4.9; 95% CI 1.3, 18.0; n = 4 children with major congenital malformations) and valproic acid (OR: 4.9; 95% CI 1.6,

Table I. Recent studies evaluating major congenital malformation (MCM) rates in the children of women with epilepsy who used antiepileptic drugs (AEDs) including valproic acid during pregnancy

Study details	Samrén et al., 1997[28]	Samrén et al., 1999[24]	Canger et al., 1999[29]	Kaneko et al., 1999[22]	Kaaja et al., 2003[30]
Region	Multinational	The Netherlands	Italy	Multinational	Finland
Inclusion period	1972–90	1972–92	1977–99	1978–91	1980–98
Total no. of patients	1221	1411	452	983	740
Study design	Prospective	Retrospective	Prospective	Prospective	Prospective
Definition of MCM	Abnormality of an essential embryonal structure that is present at birth or discovered during the first year of life	Abnormality of an essential embryonic structure or an abnormality requiring significant therapy that is present at birth or discovered during the first 6 weeks of life	Abnormality of an essential embryonic structure or an abnormality requiring special therapy (spreading device or surgery) during the first year of life	Not specified	Malformation resulting in death or one likely to cause a serious handicap or require surgery
Control group	Matched non-epileptic women	Matched unexposed women	Small group of women receiving no treatment	None	Women who were not treated in the first trimester
Case ascertainment	Yes	No	Yes	Yes	Yes
Preterm terminations	Excluded	Terminations for MCM included	Excluded	Excluded	Included
MCM rates [%] (no. patients assessed)					
overall	9 (1221)	3.7 (1411)	9.7 (452)	8.4 (983)	Not reported
no AED	Not assessed in full cohort	Not assessed	Not assessed	3 (98)	1 (239)
carbamazepine monotherapy	8 (280)[a]	4 (379)[a]	7 (113)	6 (158)	3 (363)
phenobarbital monotherapy	10 (48)	3 (172)	5 (83)	5 (91)	None reported (5)
phenytoin monotherapy	6 (41)	1 (151)	3 (31)	9 (132)	2 (124)
primidone monotherapy	9 (43)	None reported (18)	9 (35)	14 (35)[a]	17 (6)
valproic acid monotherapy	9 (184)[a]	6 (158)[a]	16 (44)[a]	11 (81)[a]	7 (61)[a]
ethosuximide monotherapy	8 (13)	None reported (9)	Not assessed	Not assessed	None reported (2)
Dose-dependence of risk (valproic acid)	High risk ≥1000 mg/d	High risk ≥1000 mg/d	1000 mg/d = no MCM Mean dosage 1712 mg/d in MCM (mean study dose = 1129 mg/d)	High risk ≥1000 mg/d (mean study dosage 823 mg/d)	Valproic acid: none observed (mean study dosage 900 mg/d)
Comments	Pooled data from five studies		MCM due to genetic and chromosomal anomalies included		Risk associated with low serum folate levels

a Incidences represent significantly higher rates than in the control group.

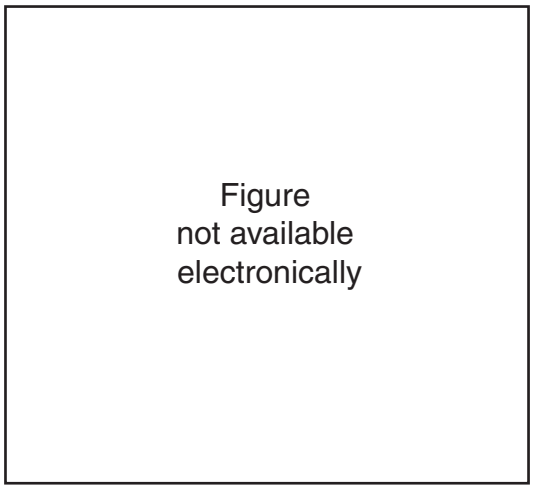

Fig. 1. Malformation rates in babies born to women taking antiepileptic drugs during pregnancy identified in six recent studies. Data for phenobarbital, phenytoin and valproic acid (sodium valproate) are presented as odds ratios and 95% confidence limits compared with the risk associated with carbamazepine (reproduced from Tomson et al.,[26] with permission).

15.0; n = 6 children with major congenital malformations) when used in monoptherapy. Using the data for all 1221 exposed children, the relative risk of a major malformation associated with exposure to the different drugs was compared against the risk associated with exposure to the drug with the lowest rate of malformations (phenytoin). However, there were no differences in the relative rates of malformations between the different drug groups. Concerning valproic acid, a significant dose-dependence was observed in the incidence of malformations, with a risk of major malformations that was 6.8-fold higher in those infants exposed to ≥1000 mg/day than in those exposed to ≤ 600 mg/day. Spina bifida was the most frequent malformation observed in valproic acid-exposed children and accounted for seven cases of malformation associated with valproic acid monotherapy in this study. Regarding the other AEDs, spina bifida was only observed in four children exposed to carbamazepine.

A subsequent and more extensive analysis of data from 28 hospital centres in the western Netherlands that included some of the subjects from the previous study has also been published.[24] The use of a standardised methodology permitted malformation rates to be estimated with improved precision and allowed the marked centre effect in the previous study to be avoided. This was a retrospective cohort study of 1411 index children born between 1972 and 1992 to mothers with epilepsy who were exposed to AEDs during the first trimester of pregnancy, compared with 2000 matched controls. Overall malformation rates were lower than those observed in the previous pooled analysis. Increased rates of major congenital abnormalities compared with unexposed infants were reported for infants exposed to carbamazepine (3.7%; 95% CI 1.8, 5.6) and valproic acid (5.7%; 95% CI 2.1, 9.3) monotherapy, with an elevated risk that did not reach statistical significance being observed for phenobarbital. Phenytoin monotherapy was not associated with an increased risk of major congenital abnormalities. Polytherapy was generally associated with higher rates of malformation. Odds ratios for major malformations between treatment groups did not demonstrate any significant differences. Once again, there was evidence for a significant dose-response relationship for the rate of malformations associated with valproic acid, whereas no such association was observed for carbamazepine. The relative risk of major congenital malformations in the children of mothers exposed to a dosage of valproic acid >1000 mg/day compared with those exposed to <600 mg/day was 3.9 (95% CI 1.4, 11.1).

Another multinational analysis used a standardised method to collect data on major congenital malformations in 983 infants exposed to AEDs *in utero* who were born in participating centres in Canada, Italy and Japan between 1978 and 1991.[22] The prospective nature of the study allowed information on potential confounding variables related to epilepsy, treatment and pregnancy to be collected systematically. For monotherapy, crude malformation rates varied from 5.1% (95% CI 0.2, 9.9) with phenobarbital to 14.3% (95% CI 2.7, 25.9) with primidone; the rate reported for valproic acid was 11.1% (95% CI 4.3, 18.0). There were no significant differences in malformation rates between the various drugs, although the rates observed for primidone (p = 0.029) and valproic acid (p = 0.039) were significantly higher than those for unexposed infants. In the case of polytherapy, a particularly striking linear relationship between the malformation rates and the number of AEDs used was observed (p = 0.012;

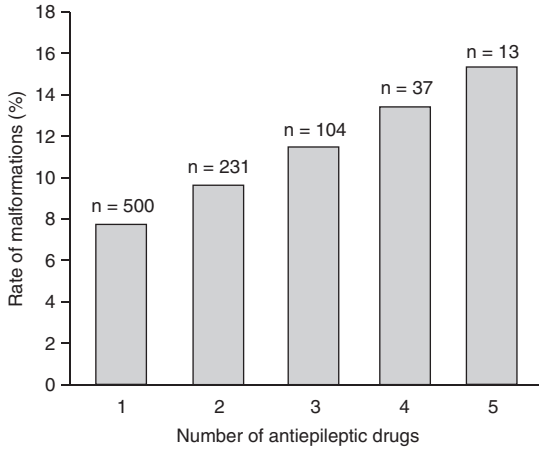

Fig. 2. Malformation rates in babies born to women taking antiepileptic drugs during pregnancy as a function of the number of antiepileptic drugs used.[22]

figure 2). Valproic acid was the only AED for which a significant dose-response relationship was demonstrated ($p = 0.0075$). The authors suggested that a daily dosage of 1000 mg/day represented an inflexion point in the dose-risk relationship curve with respect to malformations. Similarly, they suggested that there was a significant association between plasma valproic acid levels in the mother during the first trimester and malformation rates in the infant, with an inflexion point of approximately 70 µg/mL ($p = 0.005$; figure 3).

A prospective multicentre study performed in the Boston area enrolled women giving birth in maternity units between 1986 and 1993.[23] Four groups of newborns were compared: 508 born to women without epilepsy and 414 born to women with epilepsy (98 untreated, 223 receiving monotherapy and 93 receiving polytherapy). Major congenital malformation rates were higher in infants exposed to AEDs (3.7%) than in unexposed infants born to mothers with a history of seizures (no malformations observed) or with no seizure history (1.8%). Malformation rates seen with individual AEDs varied from 3.4% with phenytoin to 5.2% with carbamazepine; valproic acid was not evaluated in this study. None of the reported differences achieved statistical significance with respect to mothers without epilepsy, except for the polytherapy group.

Another prospective study was performed in a single centre in Milan.[29] The incidence of malformations among infants of mothers with epilepsy treated with AEDs during pregnancy was determined. A total of 517 pregnancies were followed, and in 25 of the pregnancies the mother did not receive AEDs. The overall rate of all types of congenital malformations in the 313 infants exposed to AED monotherapy was 10.5% (95% CI 7.1, 13.9); no such malformations were detected in the 25 unexposed infants. The highest rate was observed in infants exposed to valproic acid (15.9%; 95% CI 6.8, 29.6). However, there were significant differences in the relative rates of malformations between the valproic acid and other drug exposure groups.

The most recent study was a single-centre prospective study performed in Helsinki.[30] Malformation rates were compared between 740 infants born to women using AEDs and 239 born to untreated women between 1980 and 1998. In this study, the

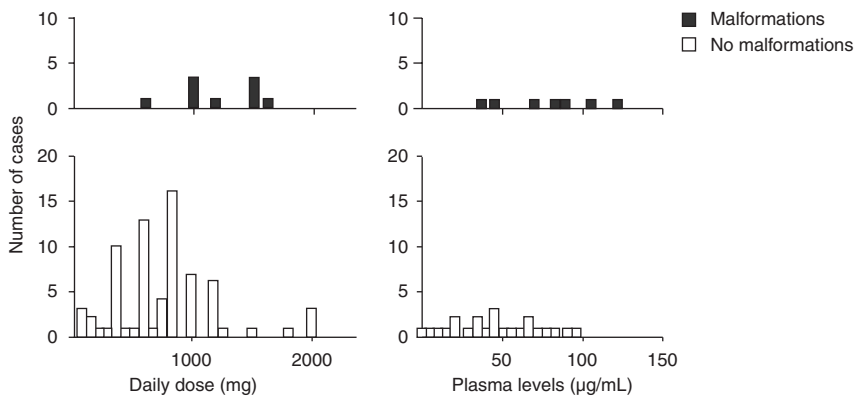

Fig. 3. Association between malformation rate and dose (left) and plasma levels (right) of valproic acid (sodium valproate).[22]

majority of AEDs were used as monotherapy (80% of pregnancies) and no distinction was made between exposure to monotherapy and polytherapy in the subsequent assessment of individual drug risks, although, as in previous studies, polytherapy was associated with a higher risk than monotherapy in general. An elevated risk compared with unexposed infants was reported for newborns exposed to carbamazepine (OR: 2.6; 95% CI 1.0, 6.0; p = 0.054; n = 455), valproic acid (OR: 4.1; 95% CI 1.6, 10.5; p = 0.003; n = 126) and oxcarbazepine (OR: 10.8; 95% CI 1.1, 106.2; p = 0.04; n = 9). In contrast to previous studies, no dose-response relationship for valproic acid was observed in this study, although the number of cases involving high dosages was low. An original finding of the study was that the risk of malformations was associated with low serum folate levels during the first trimester (OR: 5.6; 95% CI 1.2, 25.8; p = 0.02).

2.2.2 Retrospective Registry Analyses

A recent Swedish study[32] has addressed the problem of malformation rates in a rather different way. Infants exposed to AEDs *in utero* were identified by combining entries on all births to women who had reported the use of AEDs recorded in the Swedish Medical Birth Registry with data on birth defects in the Swedish Registry of Congenital Malformations. Major congenital malformations were defined using the International Classification of Diseases (9th Edition), although certain malformations considered unlikely to be related to AED exposure, such as undescended testicle, were excluded. The methodology used presents three advantages: firstly, it generates a large sample size, increasing the precision of the estimate; secondly, it ensures the most exhaustive (estimated as 70%) and representative possible sample of potential cases in Sweden; and finally, it minimises inclusion bias. However, the study also has certain limitations; for example, data on terminations of pregnancy due to fetal malformations were not available, leading to a possible underestimation of malformation rates. During the study period (1995–2001), 1398 infants had been exposed to AEDs *in utero* and 121 presented with a congenital malformation. Assuming a malformation rate in the Swedish general population of 1%, the OR for having a major malformation in the AED-exposed group was 1.86 (95% CI 1.42, 2.44) and was significantly higher in subjects exposed to AED polytherapy than AED monotherapy. For the most widely used AEDs, the observed rate of major congenital malformations was higher than the background rate in the general population, and was 4.0% for carbamazepine (n = 703), 4.4% for lamotrigine (n = 90), 6.8% for phenytoin (n = 103) and 9.7% for valproic acid (n = 268). The only intergroup difference that was statistically significant was between carbamazepine and valproic acid (OR: 2.59; 95% CI 1.43, 4.68). Potential dose-outcome relationships were not evaluated.

2.2.3 Prospective Pregnancy Registries

To address the problem of low patient numbers in such studies, several national and international epilepsy and pregnancy databases have been set up with the aim of generating a sample size sufficient to estimate relative rates of malformations with precision. Another advantage of these prospective registry studies is that malformations leading to voluntary termination of pregnancy and malformations seen in spontaneous preterm abortions are accurately represented. Obviously, this precision will increase with the rate of recruitment of subjects into the registries and the length of time the registries have been set up. Currently, none of the registries have achieved the several thousand subjects per treatment group that is required to estimate the relative risk associated with different drugs with high precision, in spite of the fact that the oldest of these has already been including patients for 8 years. Nonetheless, certain trends are already apparent and are comparable between the different registries, reinforcing the clinical relevance of the findings. A potential source of error in the estimates generated from these registries is inclusion bias, for example inclusion of patients following detection of a fetal malformation during antenatal monitoring. This would result in an overestimation of the malformation rate. To avoid such bias, inclusions should be systematic and prospective, but there is little way of ensuring that this actually occurs. Reported 'non-prospective' inclusion rates have been as high as 50%. The data on malformation rates from these registries that have been reported to date are presented in table II.

Table II. Pregnancy in epilepsy patient registry characteristics and major congenital malformation rates that have been reported in these registries, stratified according to antiepileptic drug (AED) exposure

Registry details	UKEPPR[8]	NAREP[33,34]	ARADP[35,36]	ILPR[37]
Region	UK	North America	Australia	Multinational
Inclusion period	1996–2005	1997–2004	1999–2004	1992–2004
Total number of pregnancy outcomes	3607	3708	555	414
Definition of MCM	Eurocat criteria	Abnormalities with surgical, medical or cosmetic importance. Genetic and chromosomal abnormalities excluded	BDR criteria	CDC criteria. Genetic and chromosomal abnormalities excluded
Control group	Untreated epilepsy	All hospital births	Untreated epilepsy	None
Case ascertainment	Consultation	Consultation	By telephone	By telephone
Time of inclusion	Before known outcome	Before known outcome (in principle)	Unspecified	First trimester
Outcome status at inclusion	Unknown	Unknown in 62% of cases	Not an inclusion criterion	Unknown[a]
Malformation rates [%] (no. patients assessed)				
no AED	3.5 [95% CI 1.8, 6.8] (227)	1.62	2.5 (40)	Not evaluated
carbamazepine	2.2 [95% CI 1.4, 3.4] (900)	Not reported	Not reported	Not evaluated
lamotrigine	3.2 [95% CI 2.1, 4.9] (647)	Not reported	None reported (61)	2.9 [95% CI 1.6, 5.1] (414)
phenobarbital	Not reported	6.5 [95% CI 2.4, 13.7] (92)	Not assessed	Not evaluated
valproic acid	6.2 [95% CI 4.6, 8.2] (715)	10.7 [95% CI 6.3, 16.9] (149)	16.1 (113)	Not evaluated
Risk factors	Valproic acid dose (>1000 mg/d); lamotrigine dose (>200 mg/d)	Not reported	Polytherapy; valproic acid dose (>1100 mg/d)	Polytherapy with valproic acid

a Pregnancies with known outcomes at inclusion are excluded from prevalence calculations.

ARADP = Australian Registry for Antiepileptic Drugs in Pregnancy; **BDR** = Birth Defects Registry; **CDC** = Centers for Disease Control (USA); **ILPR** = International Lamotrigine Patient Registry; **MCM** = major congenital malformation; **NAREP** = North American Registry for Epilepsy and Pregnancy; **UKEPPR** = UK Epilepsy and Pregnancy Patient Registry.

The first such registry to be established was the UKEPPR in 1996[27] and this had included 4414 women by 31 March 2005.[8] In principle, non-prospective inclusion of women whose outcome was known from antenatal screening is not permitted in this registry. The relatively long lifetime of this registry has allowed a preliminary estimation of the risk of major congenital malformations in infants exposed *in utero* to the AEDs most widely used in monotherapy compared with a reference group of babies born to untreated women with epilepsy.[8,38,39] Malformation rates observed following exposure to carbamazepine or lamotrigine monotherapy were close to the rate observed in the unexposed groups (3.5%). On the other hand, after exposure to valproic acid, the malformation rate (6.2%) was significantly higher ($p < 0.001$) than that observed in the carbamazepine group (table II). A dose-response relationship between lamotrigine dose and malformation rate ($p = 0.005$), and a non-significant trend towards such an association for valproic acid dose, were observed.

The North American Registry for Epilepsy and Pregnancy (NAREP)[48,49] was established in 1997 and had enrolled 3708 women by July 2004. Estimations of malformation rates associated with the individual AEDs are released from this registry only when their 95% confidence limits exclude the postulated 'background' malformation rate of 2%, thus demonstrating a statistically significant association. So far, estimated malformation rates have been divulged for phenobarbital[33] and valproic acid.[34] For valproic acid, the major malformation rate was 10.7%, comprising 16 affected individuals. This corresponded to a relative risk for having an affected infant of 7.3 (95% CI 4.4, 12.2; $p < 0.001$) for women with epilepsy exposed to valproic acid compared with a reference cohort of all maternity department births. The relative risk in women exposed to phenobarbital (five affected individuals) was 4.2 (95% CI 1.5, 9.4; $p = 0.001$).

An Australian registry (ARADP) was established in 1999 and had included 565 pregnancies by July 2004.[35,50] Of the four AEDs implicated (valproic acid, carbamazepine, phenytoin and lamotrigine), a malformation rate significantly different from that observed in untreated patients was only observed for valproic acid. The increased risk associated with valproic acid was clearly related to the dosage received. The mean daily dosage of valproic acid taken by women who gave birth to babies with malformations was very high; nearly twice as high as the dosages used in pregnancies with normal outcomes (1906 mg/day vs 1005 mg/day).[35] Dosages >1100 mg/day were associated with a high risk ($p < 0.001$), whereas dosages below this that were used in monotherapy were not associated with statistically significant increases in the risk of malformation.[36] Valproic acid was the only AED evaluated for which such a dose-outcome relationship was observed.

The latest registry to have been established is a European collaborative registry, EURAP.[51,52] This registry also includes the data from the previously mentioned Australian registry and India.[53] Although >4800 pregnancies have now been included in the EURAP database, no data on malformation rates have been released.

A manufacturer-sponsored pregnancy registry, the International Lamotrigine Patient Registry (ILPR), has also been set up specifically to monitor the risk of major malformations in neonates exposed to lamotrigine during the first trimester.[54] This is an international collaboration that prospectively enrols pregnant women in 31 countries. The data published from this registry[37] have indicated a malformation rate in neonates exposed to lamotrigine monotherapy of 2.9%, an identical figure to that observed in the UKEPPR. However, in 88 women receiving combination therapy with lamotrigine and valproic acid, the malformation rate rose to 12.5% (95% CI 6.7, 21.7), whereas in 182 instances of lamotrigine combination therapy involving drugs other than valproic acid, the observed rate (2.7%; 95% CI 1.0, 6.6) was similar to that observed in women receiving lamotrigine monotherapy.

3. Valproic Acid and Minor Congenital Malformations

In addition to these major congenital malformations, less severe malformations, notably facial dysmorphisms, have also been described in association with AED therapy. As discussed earlier, one of the first AEDs to be associated with a fetal syndrome was phenytoin, but it is now recognised that dysmorphic features may occur in children of mothers

who are taking other AEDs, including carbamazepine[55-57] and valproic acid.[58-63] Facial dysmorphisms associated with a fetal valproate syndrome include epicanthic folds, a flat nasal bridge, a broad nasal base, a short nose with anteverted nostrils, a shallow philtrum, a long, thin upper lip and a thick lower lip. In the absence of dedicated large retrospective or prospective studies, the absolute prevalence of the fetal valproate syndrome is not definitely known and the relative risk compared with other AEDs is poorly established. Nonetheless, data from the US suggest that polytherapy with multiple AEDs is a risk factor for fetal anticonvulsant syndrome.[63] This was also reported in a study of 57 children followed up in Scotland, where trends for more severe malformations and symptoms was seen with both maternal exposure to dosages of valproic acid of ≥1000 mg/day and exposure to multiple AEDs.[42]

In all of these fetal anticonvulsant syndromes, facial dysmorphisms may be associated with behavioural problems and retarded development. In clinical practice, the presence at birth of facial dysmorphisms that are characteristic of fetal valproate syndrome should incite the physician to follow the neuropsychological and behavioural development of the child closely, so that remedial measures can be taken as soon as possible if problems arise.

4. Valproic Acid and Developmental Delay

It was first suggested over 30 years ago that exposure to AEDs *in utero* could be associated with delayed psychomotor development in the offspring of women taking such drugs during pregnancy.[64-69] This was most commonly described in children of women with epilepsy treated with phenytoin, although a causal association between treatment and developmental delay could not be unequivocally established. Valproic acid was not specifically assessed in these early studies. The characteristics of more recent studies that have evaluated valproic acid are listed in table III. It should nevertheless be pointed out that these studies are difficult to compare because of differences in the form of testing performed and in the age at which the children were assessed.

4.1 Retrospective Studies

The first study in which data on valproic acid are available is a retrospective study of 40 children exposed *in utero* to phenobarbital, phenytoin or valproic acid monotherapy.[40] The study reported that the children who were exposed to valproic acid were the most compromised in terms of later neurological function, which was assessed using a checklist previously developed for paediatric use by Touwen.[70] In most of the affected children, the impairment was considered to be minor neurological dysfunction. Valproic acid serum concentrations at birth were correlated with the number of abnormal items on the Touwen checklist at 6 years of age.

The largest series of data on developmental outcomes in children exposed to valproic acid *in utero* has come from a retrospective study of women followed in the Mersey Regional Epilepsy Clinic in Liverpool between 1989 and 1999. Two analyses have been published from this database.[43,46] In the first analysis, questionnaires were sent to 1267 women in the database aged between 16 and 40 years. Women with other identified neurological disorders or learning difficulties were excluded. The questionnaire collected data on the seizure history, treatments and pregnancies of the women, and the educational status of their children. Information on treatments was validated from hospital records. Data were collected for 330 mothers and their 594 children aged between 3 months and 23 years. Of the 400 children attending school, 42 required remedial help. Risk factors for children with additional educational needs were estimated as ORs compared with unexposed children born to untreated mothers from the same series. Sufficient cases were available to estimate the risk associated with exposure to monotherapy with valproic acid (56 children) or carbamazepine (63 children). The OR for the association between exposure to valproic acid and additional educational needs was 3.40 (95% CI 1.63, 7.10). No such association was observed for exposure to carbamazepine.

However, as the authors pointed out, a number of potential confounding factors that could differ between treatment groups and also influence scholastic achievement, such as differences in the epilepsy syndrome, type and severity of seizures, sociodemo-

Table III. Recent studies evaluating developmental delay (DD) in the children of women with epilepsy who used antiepileptic drugs during pregnancy

Study	Country	Study period	Study type	Total no. of children	Mean valproic acid dosage (mg/d)	Incidence of DD (%)	Dose dependence (high-risk group)	Comments
Koch et al., 1996[40]	Germany	NR	Retrospective	40 (PB = 18; VPA = 9)	NR	PB: 11 VPA: 33	For VPA serum concentrations	Variable observed: minor neurological dysfunction
Wide et al., 2000[41]	Sweden	1985–95	Prospective	100 (CBZ = 48; PHT = 28; VPA = 7)	NR	Equivalent to general population	Not evaluated	Evaluation performed at age 9mo
Moore et al., 2000[42]	UK	NR	Retrospective	57 (VPA = 46)	NR	Overall: 77	Not evaluated	Only evaluated subjects with minor malformations
Adab et al., 2001[43]	UK	1975–98	Retrospective	594 (CBZ = 63; VPA = 56)	NR	Unexposed: 11 CBZ monotherapy: 3 VPA monotherapy: 30	Not evaluated	
Dean et al., 2002[44]	UK	1976–2000	Retrospective	293	NR	Unexposed: 10.5 Exposed: 24 PB: 10 VPA: 28 PHT: 33	None identified	Higher risk with polytherapy (n = 51; 38%)
Mawer et al., 2002[45]	UK	1990–99	Prospective	45 (CBZ = 18; VPA = 23)	1236	CBZ: 27.8 VPA: 34.8	VPA (≥1000 mg/d) CBZ: none	
Adab et al., 2004[46]	UK	NR	Retrospective	249 (CBZ = 52; PHT = 21; VPA = 41)	NR	CBZ: no effect PHT: no effect VPA: VIQ	VPA (>800 mg/d) CBZ: none	Low maternal IQ and generalised tonic clonic seizures during pregnancy are risk factors
Gaily et al., 2004[47]	Finland	1989–94	Retrospective	182 (CBZ = 109; VPA = 30)	1200	VPA: VIQ	VPA (p = 0.04)	

CBZ = carbamazepine; **MT** = monotherapy; **NR** = not reported; **PB** = phenobarbital; **PHT** = phenytoin; **VIQ** = verbal IQ; **VPA** = valproic acid.

graphic status, mother tongue, parental IQ or maternal education, were not taken into account.[43] This limitation was partially addressed in a subsequent analysis of this database,[46] in which more detailed information on both the mothers and the children was obtained by semi-structured interviews. Assessments of IQ and neuropsychological functioning were also performed in the children. Data were available for 249 children of school age, of whom 41 had been exposed to valproic acid. Verbal IQ was significantly lower in children exposed to valproic acid than in those exposed to carbamazepine or phenytoin and unexposed children, and the OR for having a verbal IQ of ≤69 in valproic acid-exposed children compared with untreated children was 3.5 (95% CI 1.1, 10.6).[46] Determinants of verbal IQ were assessed by multivariate regression analysis, which identified low maternal IQ, multiple tonic-clonic seizures during pregnancy and exposure to valproic acid as being independent determinants of IQ. There was some suggestion that the association of low IQ with valproic acid exposure might be dose-related (figure 4), with the verbal IQ of children exposed to doses of valproic acid of ≤800 mg/day being similar to that of unexposed children. Nonetheless, this second analysis does not resolve all of the potential ambiguities associated with the retrospective methodology used, notably the low response rate (40%) and the potential inclusion and recall biases. The true impact of valproic acid and other AEDs on development will only be able to be ascertained unequivocally from large, carefully planned and implemented prospective studies.[71]

Verbal IQ was also assessed in a study performed in Finland[47] that evaluated 189 children born to mothers with epilepsy in Helsinki between 1989 and 1994 and 121 age-matched controls born in the same hospital. The number of mothers treated with valproic acid during pregnancy was low: 13 monotherapy and 17 polytherapy recipients. The majority of the index cases had been exposed to carbamazepine. A reduced mean verbal IQ was reported for children exposed *in utero* to valproic acid compared with those exposed to carbamazepine or to matched controls. Again, a negative association was observed between valproic acid dosage and verbal IQ; the higher the dosage, the lower the verbal IQ ($p = 0.04$).

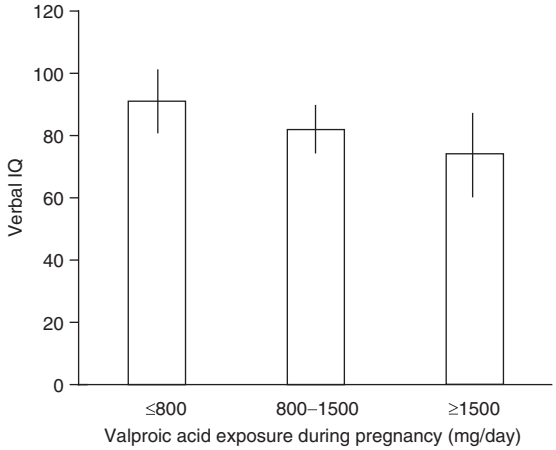

Fig. 4. Verbal IQ of children exposed to valproic acid (sodium valproate) *in utero* as a function of valproic acid dose during pregnancy.[46]

Another population-based study evaluated outcomes in 293 children of 149 women treated for epilepsy who had given birth in the Aberdeen Maternity Hospital in Scotland between 1976 and 2000.[44] Developmental delays were observed in 24% of exposed children compared with 10.5% of unexposed children. For individual AEDs, the proportion of children with developmental delay varied from 10% for phenobarbital to 33% for phenytoin (28% for valproic acid). The use of polytherapy was associated with an even higher risk of developmental delay (38%). Developmental impairment of the children was also associated with a family history of developmental delay, which suggests that an interaction between AED exposure and other susceptibility factors may be important.

4.2 Prospective Studies

A prospective study performed in Sweden followed 100 children born to mothers who received AEDs during pregnancy; however, only seven cases concerned exposure to valproic acid.[41] This study evaluated psychomotor development at 9 months of age using the Griffiths test and found no difference in scores between the study cohort and matched unexposed controls, even for the subgroup of 21 children exposed *in utero* to phenytoin. The study also evaluated the emergence of minor congenital abnormalities and observed an increased risk associ-

ated with carbamazepine treatment, but no increased risk associated with the other drugs studied (OR 11.0; 95% CI 1.42, 85.2; n = 39). A contemporary, but retrospective study[42] evaluated intellectual performance in 57 children with a fetal anticonvulsant syndrome characterised by facial dysmorphism and other minor malformations, of whom the majority (80%) had been exposed to valproic acid; 34 to monotherapy and 12 to polytherapy. Exposure to carbamazepine and phenytoin was reported in 19% and 16% of the subjects, respectively, either as monotherapy or as polytherapy. Exposure to AEDs other than valproic acid, carbamazepine or phenytoin was only reported when they were used in association with one of these three AEDs. A developmental delay or learning difficulties were observed in 77% of the study group. Information on exposure to individual AEDs in these subjects was not reported.

The only long-term prospective study of developmental outcomes corresponds to a cohort of 45 children born to mothers with epilepsy who were followed at the Manchester Royal Infirmary between 1990 and 1999.[45] A developmental delay was observed in 8 of 23 children exposed to valproic acid monotherapy *in utero*. There was a suggestion of a positive association between developmental outcome and valproic acid dosage, as the higher the valproic acid dose the poorer the developmental outcome, although this was not of statistical significance (p = 0.06). At dosages of 1000 mg/day, impairment was absent or mild, whereas it was moderate or severe in approximately half of the children exposed to higher doses. Interestingly, the subsequent pregnancies of three women treated with a high dose of valproic acid who had given birth to children with severe developmental delay resulted in healthy children following a reduction in dosage (two cases) or the withdrawal (one case) of valproic acid. A developmental impact was also observed in 5 of 15 children exposed to carbamazepine monotherapy, although, in this case, no relationship with the dosage was observed.

4.3 Autism

Autistic symptoms have been described in case histories of children exposed *in utero* to valproic acid,[61,72,73] as well is in the case series from Aberdeen described previously.[44] However, the interpretation of these reports is confounded by the lack of consistent diagnostic criteria for the definition of autism. A more quantitative and reliable estimate of this risk has come from a subsequent prospective study reported by the Aberdeen group, who evaluated 626 children exposed *in utero* to AEDs.[74] Valproic acid was the drug most commonly associated with autistic disorder and corresponded to 45% of the identified cases of autism. Five of 56 (8.9%) of the study children exposed to valproic acid monotherapy fulfilled Diagnostic and Statistical Manual of Mental Disorders-IV diagnostic criteria for autistic disorder or Asperger syndrome.

4.4 Systematic Reviews and Perspectives

A recent review of all published data on the developmental outcomes of the children of mothers exposed to AEDs during pregnancy performed for the Cochrane database[75] concluded that there were insufficient data available to advise women about the risks of individual AEDs with respect to their children's development and cognition and that, based on the available evidence, it would be advisable for women to continue optimised AED medication during pregnancy in order to achieve adequate seizure control. Nonetheless, the available evidence clearly points to an increased risk of developmental delay in the children of women with epilepsy who use valproic acid during pregnancy. The severity of this syndrome can range from a mild reduction in age-matched IQ to full autism. However, quantification of this risk, and notably assessment of the impact of potential treatment-unrelated confounding factors, requires more rigorous evaluation in a dedicated prospective study.

5. Managing Pregnancies in Patients Treated with Valproic Acid

5.1 Initiation of Valproic Acid Treatment in Women of Childbearing Potential

When AED treatment is first initiated in women of childbearing age, the potential impact on reproductive health in general, and the risk of fetal harm in particular, should be considered in the choice of treatment. In many cases, an equally effective alter-

native to valproic acid may be available and should be considered as a first-line treatment. In other cases, for example in juvenile myoclonic epilepsy, such alternatives may not exist. If initiation of valproic acid treatment is considered appropriate in women with epilepsy, the future reproductive potential of the patient needs to be taken into account, regardless of the age of the patient.[76] For all women of reproductive age, it is important to consider the treatment regimen, appropriate contraception and pregnancy planning. The issues related to valproic acid treatment in pregnancy need to be presented to the patient in an objective way that is adapted to the educational level of the patient. At the same time, the patient needs to be reassured that, if appropriate precautionary measures are taken, the chances of having a trouble-free pregnancy and a healthy baby are very high. A trusting relationship between patient and physician, in which appropriate counselling can be offered, needs to established and sustained throughout the treatment duration. Appropriate information should be provided to enable the patient to plan pregnancies and optimise their outcomes. Regular counselling sessions should be proposed so that the advice provided can be adapted to the current clinical, emotional and social context of the patient.

If the decision is made that valproic acid should be continued, despite the risks, patients should, wherever possible, be treated with the lowest dosage valproic acid monotherapy that can adequately control seizures, and preferably with a dosage <1000 mg/day.[77] Preclinical data have shown that high plasma concentrations of valproic acid are potentially associated with an increased teratogenic risk,[78] although this has not been investigated in humans. High peak plasma concentrations may be avoided by use of a sustained-release formulation[79] and this may be a suitable precautionary measure to reduce the risk of adverse outcomes in women with epilepsy. However, it should be pointed out that there are no data available that compare pregnancy outcomes in women using sustained-release formulations with those in women using immediate-release formulations.

It should be borne in mind when considering the initiation of valproic acid treatment in women of reproductive age that even though pregnancies should ideally be planned, they are often unplanned and, for this reason, a treatment regimen with the lowest risk to any future pregnancy should be chosen wherever possible from the moment that valproic acid is initiated.

5.2 Planning a Pregnancy

Optimal management should address concerns about safety but not lose sight of the primary treatment objective, which is the prevention of seizures. Management should aim to increase overall quality of life, which is determined both by seizure frequency and treatment-related adverse effects.[80] It is important to carefully consider the relative risk of harm to the mother or fetus, which is attributable, on the one hand, to the AED and, on the other hand, to the potential loss of seizure control.

Familial and personal antecedents should be taken into consideration. If the mother has already given birth to one affected child with valproic acid-related embryopathy, a change in drug treatment from valproic acid to another AED should be undertaken whenever possible. There is some evidence that there may be a genetic susceptibility to valproic acid-induced fetal abnormalities. For example, an increased rate of fetal valproate syndrome has been associated with mutations in the methyltetrahydrofolate reductase gene.[81] This should be explored more thoroughly in future studies, in order to provide specific recommendations for genetic testing.

When a pregnancy is planned, treatment should be reassessed and the risks and benefits of alternative AED regimens evaluated carefully. In all cases, the most appropriate drug for providing optimal seizure control for the given seizure type and epilepsy syndrome should be considered first. If the decision is made that valproic acid should be continued, despite the risks, patients should be treated, wherever possible, with the lowest dosage valproic acid monotherapy that will adequately control seizures and, wherever possible, with a dose <1000 mg/day.[77] Whatever the treatment, the importance of compliance with therapy throughout pregnancy needs to be clearly communicated to the patient.

It is important to convince patients to plan their pregnancies. Once the decision to attempt to become pregnant has been made, the physician needs to

discuss with the patient all relevant management issues that arise, including the advisability of continuing valproic acid treatment, and to implement any changes to treatment that may be necessary.

If women are not already treated with the lowest risk regimen possible, i.e. monotherapy at the lowest possible dosage required to achieve satisfactory seizure control, a switch to monotherapy should always be considered. If it is decided that the patient should continue valproic acid, dosages >1000 mg/day should be avoided. As a precautionary measure, splitting of the dosage into multiple doses per day may be useful, and the use of sustained release formulations should be considered, although there is no hard evidence for the benefit of such practices. A switch from valproic acid to another AED with a lower teratogenic risk could be envisaged, although there is little consensus or evidence from studies to guide such decisions. It is important to initiate these changes well before conception, ideally 6–12 months before, in order to verify that seizure control is satisfactory before conception.[82] Changes in treatment after conception should be avoided as it will be too late to significantly reduce any risk of congenital malformations and there will be a risk of loss of seizure control.

5.3 Folic Acid Supplementation

The risk of neural tube defects may be reduced by folic acid supplementation. Although this has been demonstrated in the general population,[83] no specific studies have been performed in women with epilepsy who are being treated with either valproic acid in particular, or AEDs in general. However, some,[84-87] but not all,[88] animal studies have demonstrated that folic acid supplementation can prevent the failure of neural tube closing that is associated with valproic acid administration in mice. There is inconsistent evidence that valproic acid modifies plasma folate levels in humans,[89] with some studies showing a reduction of folic acid absorption or plasma levels[90-92] and others failing to demonstrate such an effect.[93-96] Nonetheless, the ability of valproic acid and other AEDs to inhibit the absorption of folic acid and reduce endogenous folic acid levels provides not only a feasible explanation for the occurrence of neural tube defects but also a rationale for the use of folic acid supplementation in pregnant women using this drug.[97,98]

However, a case report of a child born with spina bifida to a mother taking valproic acid 2000 mg/day despite adequate folic acid supplementation[99] cautions against considering that folic acid supplementation provides complete protection against neural tube defects. In addition, in all 16 instances described in the NAREP where babies with congenital malformations were born to mothers taking valproic acid, the mothers were also receiving folic acid supplementation.[34]

Recent consensus guidelines recommend folic acid supplementation for all women with epilepsy, regardless of whether they are being treated with valproic acid or not.[82,100,101] It is important to initiate folic acid supplementation before conception in order to achieve effective serum concentrations before the neural tube closes (22–28 days of development) and to maintain these up until the 12th week after conception. There is some evidence that valproic acid inhibits folic acid absorption, although not all studies have shown this. For this reason, as a precautionary measure, higher dosages of folic acid (2.5–5 mg/day) should be given than those recommended for the general population.[89,102] However, it should be emphasised that there is currently no evidence that such folic acid supplementation exerts any protective effect against valproic acid-associated congenital malformations in the children of women with epilepsy.

5.4 Monitoring During Pregnancy

Careful monitoring of women during pregnancy is essential to minimise all risk to the mother and the fetus. Maintenance of seizure control is extremely important. The mother should be closely monitored for an increase in seizure frequency, an occurrence that is observed during pregnancy in a considerable proportion (17–37%) of women with epilepsy.[100,103] This may be because of alterations in seizure threshold due to endocrine changes, a fall in AED exposure, decreased absorption of AEDs from the gastrointestinal tract or reduced compliance with treatment. It is important for the physician to emphasise the need for treatment compliance in order to maintain good seizure control. If nausea and vomiting are problematic, the use of a microsphere

formulation of valproic acid may allow more flexible administration with respect to diet. In the case of emergence of seizures or an increase in seizure rate, it may be necessary to adapt treatment, either by increasing the dose or introducing another treatment. However, wherever possible, modifications to the treatment regimen during pregnancy should be avoided. If treatment is adjusted, this needs to be normalised promptly *post partum*.

It has been recommended that both free and total plasma levels of valproic acid should be monitored throughout pregnancy. Baseline plasma levels need to be established before conception and then measurements should repeated if clinically justified. Although this drug is extensively protein bound, and plasma protein binding is known to decrease in pregnancy, a fall in plasma free drug concentrations during pregnancy has not been observed for valproic acid, in contrast to most of the other first-line treatments for epilepsy.[77,104,105]

Given the risk of congenital malformations with valproic acid, rigorous antenatal monitoring of the fetus is necessary.[106,107] High-resolution ultrasonography performed between weeks 11 and 13 can detect neural tube defects and scans performed up to the 20th week may detect other problems such as cardiac or facial malformations.[100] Ultrasonography will detect major malformations with high sensitivity and specificity, including >90% of neural tube defects, as well as a high proportion of cardiac malformations, skeletal defects and orofacial clefts.[108] Measurement of serum α-fetoprotein at week 15 is also useful for detecting defective neural tube closing, although abnormal levels are only informative in cases where cutaneous closing has failed.[102] Amniocentesis, which carries a risk of inducing spontaneous abortion, is not recommended unless there is another specific reason for performing this.

6. Perinatal Considerations

There are no specific issues associated with valproic acid concerning labour, delivery, birth and the immediate post-natal period. Plasma levels of valproic acid do not fall significantly during pregnancy,[105] so there is usually no need to adjust the dose following birth unless there is some specific clinical justification. Moreover, the potential for drug interactions with valproic acid is relatively low, so there are no contraindications to the use of peridural anaesthetics.

Although there is some data to suggest an increased risk of pre-eclampsia in pregnant women with epilepsy,[109,110] no specific risk has been described in women treated with valproic acid. However, as in all pregnancies, blood pressure should be monitored closely.

Valproic acid does not induce the CYP enzymes responsible for metabolising vitamin K, so this drug would not be expected to decrease plasma vitamin K levels. Although there is a theoretical risk of increased bleeding during delivery because of thrombocytopenia,[111] this has never been reported in women with epilepsy. Moreover, no bleeding complications have been reported in subjects treated with valproic acid when undergoing epilepsy surgery.[112] Supplementation with vitamin K (10mg oral daily dosage) during the last trimester of pregnancy is recommended for all pregnant women with epilepsy,[82] but there is no evidence that this is useful in patients receiving valproic acid, unlike what may be observed in certain patients receiving enzyme-inducing AEDs.[113] In addition, coagulation status should be checked in the mother before delivery, and the fibrinogen level, platelet count and coagulation time should be determined in a sample of umbilical blood after birth.

Concerning lactation, the levels of valproic acid excreted into breast milk are relatively low (≤10%) compared with many other AEDs.[114] For this reason, breastfeeding can be considered for mothers treated with valproic acid monotherapy, since the exposure of the neonate will be minimal and unlikely to be problematic. Any drug absorbed into the breast milk in fact ensures that the baby is slowly withdrawn from valproic acid exposure.

7. Conclusions

Although valproic acid is usually recognised as an effective first-line treatment for many seizure types and epilepsy syndromes, risks have been identified when this drug is used during pregnancy, notably with respect to congenital malformations and post-natal developmental delay. It has been difficult to quantify this risk but, for congenital

malformations, it probably lies somewhere between 2- and 3-fold the risk observed in children of untreated women with epilepsy. Several studies have demonstrated that the risk of both congenital malformations and post-natal developmental delay is increased with the use of valproic acid dosages >1000 mg/day or with use of this drug in polytherapy. However, this risk needs to be weighed against effective seizure control, which is also an important objective in women with epilepsy who become pregnant, as the occurrence of seizures during pregnancy carries risks both for the mother and the fetus. Other AED treatments should be used in preference if equivalent efficacy can be expected, but no specific recommendations can be made as medication should be individualised for each patient. If treatment with valproic acid is considered to be the most appropriate way to achieve optimal seizure control, for example in juvenile myoclonic epilepsy, a number of measures can be implemented to minimise risk to the fetus, such as using the lowest effective dose of valproic acid monotherapy (avoiding dosages >1000 mg/day). In spite of the lack of evidence, adequate folic acid supplementation before conception and during the first trimester may be a useful precautionary measure. There are no specific concerns associated with the use of valproic acid monotherapy during lactation. Regular counselling by the neurologist is a prerequisite for informed planning of pregnancies and optimisation of the probability of a healthy outcome in women with epilepsy.

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References

1. Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester (MN). Mayo Clin Proc 1996; 71: 576-86
2. Sander JW. The epidemiology of epilepsy revisited. Curr Opin Neurol 2003; 16: 165-70
3. Groupe CAROLE (Coordination Active du Reseau Observatoire Longitudinal de l'Epilepsie). Treatment of newly diagnosed epileptic crises: a French experience. Rev Neurol 2001; 157: 1500-12
4. Moran NF, Poole K, Bell G, et al. Epilepsy in the United Kingdom: seizure frequency and severity, anti-epileptic drug utilization and impact on life in 1652 people with epilepsy. Seizure 2004; 13: 425-33
5. Semah F, Picot MC, Derambure P, et al. The choice of antiepileptic drugs in newly diagnosed epilepsy: a national French survey. Epileptic Disord 2004; 6: 255-65
6. Thomas P, Genton P, Gelisse P, et al. Juvenile myoclonic epilepsy. In: Roger J, Bureau M, Dravet C, et al., editors. Epileptic syndromes in infancy, childhood and adolescence. 3rd ed. Eastleigh: John Libbey & Co Ltd, 2002: 335-55
7. Janz D, Dam M, Richens A. Epilepsy, pregnancy and the child. NewYork: Raven, 1982
8. Morrow JI, Russell A, Gutherie E, et al. Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 2005 Sep 12 [Epub ahead of print]
9. Crawford P. Epilepsy and pregnancy. Seizure. 2002; 11 Suppl. A: 212-9
10. Barrett C, Richens A. Epilepsy and pregnancy: report of an Epilepsy Research Foundation Workshop. Epilepsy Res 2003; 52: 147-87
11. Patsalos PN. Pharmacokinetic and pharmacodynamic interactions: principles and interpretative pitfalls. Epileptologia 1998; 6: 9-19
12. Crawford P. Interactions between antiepileptic drugs and hormonal contraception. CNS Drugs 2002; 16: 263-72
13. Blum D, Sidhu J, Bulsara S, et al. A bi-directional pharmacokinetic interaction study of lamotrigine and the combined oral contraceptive (COC) pill in healthy subjects. American Pain Society 2005, Abstract 901
14. Sabers A, Buchholt JM, Uldall P, et al. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res 2001; 47: 151-4
15. Sabers A, Ohman I, Christensen J, et al. Oral contraceptives reduce lamotrigine plasma levels. Neurology 2003; 61: 570-1
16. Shorvon SD, Tallis RC, Wallace HK. Antiepileptic drugs: coprescription of proconvulsant drugs and oral contraceptives. A national study of antiepileptic drug prescribing practice. J Neurol Neurosurg Psychiatry 2002; 72: 114-5
17. Krauss GL, Brandt J, Campbell M, et al. Antiepileptic medication and oral contraceptive interactions: a national survey of neurologists and obstetricians. Neurology 1996; 46: 1534-9
18. Crawford P, Chadwick D, Cleland P, et al. The lack of effect of sodium valproate on the pharmacokinetics of oral contraceptive steroids. Contraception 1986; 33: 23-9
19. Hanson JW, Smith DW. The fetal hydantoin syndrome. J Pediatr 1975 Aug; 87 (2): 285-90
20. Lindhout D, Omtzigt JG. Pregnancy and the risk of teratogenicity. Epilepsia 1992; 33 Suppl. 4: S41-8
21. Nulman I, Scolnik D, Chitayat D, et al. Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. Am J Med Genet 1997; 68: 18-24

22. Kaneko S, Battino D, Andermann E, et al. Congenital malformations due to antiepileptic drugs. Epilepsy Res 1999; 33: 145-58
23. Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001; 344: 1132-8
24. Samrén EB, van Duijn CM, Christiaens GC, et al. Antiepileptic drug regimens and major congenital abnormalities in the offspring. Ann Neurol 1999; 46: 739-46
25. Fried S, Kozer E, Nulman I, et al. Malformation rates in children of women with untreated epilepsy: a meta-analysis. Drug Saf 2004; 27: 197-202
26. Tomson T, Perucca E, Battino D. Navigating toward fetal and maternal health: the challenge of treating epilepsy in pregnancy. Epilepsia 2004; 45: 1171-5
27. Craig JJ, Morrow JI. New antiepileptic drugs: register of women who take the drugs during pregnancy has been set up [letter]. BMJ 1997; 314: 603
28. Samrén EB, van Duijn CM, Koch S, et al. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. Epilepsia 1997; 38: 981-90
29. Canger R, Battino D, Canevini MP, et al. Malformations in offspring of women with epilepsy: a prospective study. Epilepsia 1999; 40: 1231-6
30. Kaaja E, Kaaja R, Hiilesmaa V. Major malformations in offspring of women with epilepsy. Neurology. 2003; 60: 575-9
31. Bergmann A, Schmidt D, Hutt HG, et al. Epilepsy treatment with sustained-release formulation of valproate: experience with 1172 patients. Akt Neurol 1999; 26: 1-5
32. Wide K, Winbladh B, Kallen B. Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid: a nation-wide, population-based register study. Acta Paediatr 2004; 93: 174-6
33. Holmes LB, Wyszynski DF, Lieberman E. The AED (antiepileptic drug) pregnancy registry: a 6-year experience. Arch Neurol 2004; 61: 673-8
34. Wyszynski DF, Nambisan M, Surve T, et al. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005; 64: 961-5
35. Vajda FJ, O'Brien TJ, Hitchcock A, et al. The Australian registry of anti-epileptic drugs in pregnancy: experience after 30 months. J Clin Neurosci 2003; 10: 543-9
36. Vajda FJ, O'Brien TJ, Hitchcock A, et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. J Clin Neurosci 2004; 11: 854-8
37. Cunnington M, Tennis P, International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Lamotrigine and the risk of malformations in pregnancy. Neurology 2005; 64: 955-60
38. Russell AJ, Craig JJ, Morrison P, et al. UK epilepsy and pregnancy group [abstract]. Epilepsia 2004; 45: 1467
39. Craig JJ, Russell A, Parsons L, et al. The UK Epilepsy and Pregnancy Register: update of results 1996-2003 [abstract]. Epilepsia 2004; 45 Suppl. 7: 229
40. Koch S, Jager-Roman E, Losche G, et al. Antiepileptic drug treatment in pregnancy: drug side effects in the neonate and neurological outcome. Acta Paediatr 1996; 85: 739-46
41. Wide K, Winbladh B, Tomson T, et al. Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. Dev Med Child Neurol 2000; 42: 87-92
42. Moore SJ, Turnpenny P, Quinn A, et al. A clinical study of 57 children with fetal anticonvulsant syndromes. J Med Genet 2000; 37: 489-97
43. Adab N, Jacoby A, Smith D, et al. Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2001; 70: 15-21
44. Dean JC, Hailey H, Moore SJ, et al. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. J Med Genet 2002; 39: 251-9
45. Mawer G, Clayton-Smith J, Coyle H, et al. Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate. Seizure 2002; 11: 512-8
46. Adab N, Kini U, Vinten J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004; 75: 1575-83
47. Gaily E, Kantola-Sorsa E, Hiilesmaa V, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004; 62: 28-32
48. Holmes LB, Wyszynski DF. North American Antiepileptic Drug Pregnancy Registry [abstract]. Epilepsia 2004; 45: 1465
49. A North American Registry for Epilepsy and Pregnancy: a unique public/private partnership of health surveillance. Epilepsia 1998; 39: 793-8
50. Vajda F, Lander C, O'Brien T, et al. Australian Pregnancy Registry of Women taking antiepileptic drugs [abstract]. Epilepsia 2004; 45: 1466
51. Beghi E, Annegers JF; Collaborative Group for the Pregnancy Registries in Epilepsy. Pregnancy registries in epilepsy. Epilepsia 2001; 42: 1422-5
52. Tomson T, Battino D, Bonizzoni E, et al. EURAP: an international registry of antiepileptic drugs and pregnancy. Epilepsia 2004; 45: 1463-4
53. Thomas SV, Indrani L, Devi GC, et al. Pregnancy in women with epilepsy: preliminary results of Kerala registry of epilepsy and pregnancy. Neurol India 2001; 49: 60-6
54. Tennis P, Eldridge RR, International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Preliminary results on pregnancy outcomes in women using lamotrigine. Epilepsia 2002; 43: 1161-7
55. Nulman I, Laslo D, Koren G. Treatment of epilepsy in pregnancy. Drugs 1999; 57: 535-44
56. Jones KLJ, Lacro RV, Johnson KA, et al. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. N Engl J Med 1989; 320: 1661-6
57. Vestermark V, Vestermark S. Teratogenic effect of carbamazepine. Arch Dis Child 1991; 66: 641-2
58. DiLiberti JH, Farndon PA, Dennis NR, et al. The fetal valproate syndrome. Am J Med Genet 1984; 19: 473-81
59. Winter RM, Donnai D, Burn J, et al. Fetal valproate syndrome: is there a recognisable phenotype? J Med Genet 1987; 24: 692-5
60. Thisted E, Ebbesen F. Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. Arch Dis Child 1993; 69 (3 Special No): 288-91
61. Christianson AL, Chesler N, Kromberg JG. Fetal valproate syndrome: clinical and neuro-developmental features in two sibling pairs. Dev Med Child Neurol 1994; 36: 361-9
62. Clayton-Smith J, Donnai D. Fetal valproate syndrome. J Med Genet 1995; 32: 724-7
63. Ardinger HH, Atkin JF, Blackston RD, et al. Verification of the fetal valproate syndrome phenotype. Am J Med Genet 1988; 29: 171-85
64. Shapiro S, Hartz SC, Siskind V, et al. Anticonvulsants and parental epilepsy in the development of birth defects. Lancet 1976; I (7954): 272-5
65. Hanson JW, Myrianthopoulos NC, Harvey MA, et al. Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr 1976; 89: 662-8

66. Gaily E, Kantola-Sorsa E, Granstrom ML. Intelligence of children of epileptic mothers. J Pediatr 1988; 113: 677-84
67. Gaily E, Kantola-Sorsa E, Granstrom ML. Specific cognitive dysfunction in children with epileptic mothers. Dev Med Child Neurol 1990; 32: 403-14
68. Scolnik D, Nulman I, Rovet J, et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA 1994; 271: 767-70
69. Koch S, Titze K, Zimmermann RB, et al. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia 1999; 40: 1237-43
70. Touwen BCL. Examination of the child with minor neurological dysfunction. Clin Dev Med 1979; 71: 1-72
71. Shorvon SD. Longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004; 75: 1517-8
72. Williams PG, Hersh JH. A male with fetal valproate syndrome and autism. Dev Med Child Neurol 1997 Sep; 39 (9): 632-4
73. Williams G, King J, Cunningham M, et al. Fetal valproate syndrome and autism: additional evidence of an association. Dev Med Child Neurol 2001 Mar; 43 (3): 202-6
74. Rasalam AD, Hailey H, Williams JH, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 2005 Aug; 47 (8): 551-5
75. Adab N, Tudur SC, Vinten J, et al. Common antiepileptic drugs in pregnancy in women with epilepsy. Cochrane Database Syst Rev 2004; (3): CD004848
76. Tettenborn B, Genton P, Polson D. Epilepsy and women's issues: an update. Epileptic Disord 2002; 4 Suppl. 2: S23-31
77. Royal College of Physicians. Adults with poorly controlled epilepsy: clinical guidelines for treatment and practical tools for aiding epilepsy management. London: Royal College of Physicians, 1997
78. Nau H, Spielmann H. Embryotoxicity testing of valproic acid. Lancet 1983 Apr 2; 1 (8327): 763-4
79. Barre J, Berger Y. Pharmacokinetics of a newly developed sustained-release form of sodium valproate. In: Chadwick D, editor. Proceedings of the Fourth International Symposium on Sodium Valproate and Epilepsy, International Congress and Symposium Series No. 152. London: Royal Society of Medicine Services, 1989: 178-84
80. Berto P. Quality of life in patients with epilepsy and impact of treatments. Pharmacoeconomics 2002; 20 (15): 1039-59
81. Dean JC, Moore SJ, Osborne A, et al. Fetal anticonvulsant syndrome and mutation in the maternal MTHFR gene. Clin Genet 1999 Sep; 56 (3): 216-20
82. Quality Standards Committee of the American Academy of Neurology. Practice parameter: management issues for women with epilepsy (summary statement). Report of the quality standards committee of the American Academy of Neurology. Neurology 1998; 51: 944-8
83. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991; 338: 131-7
84. Padmanabhan R, Shafiullah MM. Amelioration of sodium valproate-induced neural tube defects in mouse fetuses by maternal folic acid supplementation during gestation. Congenit Anom (Kyoto) 2003; 43: 29-40
85. Elmazar MM, Thiel R, Nau H. Effect of supplementation with folinic acid, vitamin B6, and vitamin B12 on valproic acid-induced teratogenesis in mice. Fundam Appl Toxicol 1992 Apr; 18 (3): 389-94
86. Trotz M, Wegner C, Nau H. Valproic acid-induced neural tube defects: reduction by folinic acid in the mouse. Life Sci 1987 Jul 6; 41 (1): 103-10
87. Dawson JE, Raymond AM, Winn LM. Folic acid and pantothenic acid protection against valproic acid-induced neural tube defects in CD-1 mice. Toxicol Appl Pharmacol 2005 Aug 19 [Epub ahead of print]
88. Hansen DK, Grafton TF, Dial SL, et al. Effect of supplemental folic acid on valproic acid-induced embryotoxicity and tissue zinc levels in vivo. Teratology 1995 Nov; 52 (5): 277-85
89. Hernandez-Diaz S, Werler MM, Walker AM, et al. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000; 343: 1608-14
90. Hendel J, Dam M, Gram L, et al. The effects of carbamazepine and valproate on folate metabolism in man. Acta Neurol Scand 1984 Apr; 69 (4): 226-31
91. Goggin T, Gough H, Bissessar A, et al. A comparative study of the relative effects of anticonvulsant drugs and dietary folate on the red cell folate status of patients with epilepsy. Q J Med 1987 Nov; 65 (247): 911-9
92. Karabiber H, Sonmezgoz E, Ozerol E, et al. Effects of valproate and carbamazepine on serum levels of homocysteine, vitamin B12, and folic acid. Brain Dev 2003 Mar; 25 (2): 113-5
93. Bentsen KD, Gram L, Veje A. Serum thyroid hormones and blood folic acid during monotherapy with carbamazepine or valproate: a controlled study. Acta Neurol Scand 1983 Apr; 67 (4): 235-41
94. Gidal BE, Tamura T, Hammer A, et al. Blood homocysteine, folate and vitamin B-12 concentrations in patients with epilepsy receiving lamotrigine or sodium valproate for initial monotherapy. Epilepsy Res 2005 May; 64 (3): 161-6
95. Kishi T, Fujita N, Eguchi T, et al. Mechanism for reduction of serum folate by antiepileptic drugs during prolonged therapy. J Neurol Sci 1997 Jan; 145 (1): 109-12
96. Geda G, Caksen H, Icagasioglu D. Serum lipids, vitamin B12 and folic acid levels in children receiving long-term valproate therapy. Acta Neurol Belg 2002 Sep; 102 (3): 122-6
97. Ogawa Y, Kaneko S, Otani K, et al. Serum folic acid levels in epileptic mothers and their relationship to congenital malformations. Epilepsy Res 1991; 8: 75-8
98. Dansky LV, Rosenblatt DS, Andermann E. Mechanisms of teratogenesis: folic acid and antiepileptic therapy. Neurology 1992; 42 Suppl. 5: 32-42
99. Craig J, Morrison P, Morrow J, et al. Failure of periconceptual folic acid to prevent a neural tube defect in the offspring of a mother taking sodium valproate. Seizure 1999; 8: 253-4
100. Delgado-Escueta AV, Janz D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. Neurology 1992; 42 Suppl. 5: 149-60
101. Crawford P, Appleton R, Betts T, et al. Best practice guidelines for the management of women with epilepsy. The Women with Epilepsy Guidelines Development Group. Seizure 1999; 8: 201-17
102. Yerby MS. Management issues for women with epilepsy: neural tube defects and folic acid supplementation. Neurology 2003; 61 Suppl. 2: S23-6
103. Yerby MS, Kaplan P, Tran T. Risks and management of pregnancy in women with epilepsy. Cleve Clin J Med 2004; 71: S25-37
104. Perucca E, Crema A. Plasma protein binding of drugs in pregnancy. Clin Pharmacokinet 1982; 7: 336-52
105. Yerby MS, Friel PN, McCormick K. Antiepileptic drug disposition during pregnancy. Neurology 1992; 42 (4 Suppl. 5): 12-6
106. Malone FD, D'Altone ME. Drugs in pregnancy: anticonvulsants. Semin Perinatol 1997; 21: 114-23
107. Kennedy D, Koren G. Valproic acid use in psychiatry: issues in treating women of reproductive age. J Psychiatry Neurosci 1998; 23: 223-8
108. Shorvon S. Antiepileptic drug therapy during pregnancy: the neurologist's perspective. J Med Genet 2002; 39: 248-50

109. Yerby M, Koepsell T, Daling J. Pregnancy complications and outcomes in a cohort of women with epilepsy. Epilepsia 1985; 26: 631-5
110. Sabers A. Complications during pregnancy and delivery. In: Janz D, Dam M, Richens A, et al., editors. Epilepsy, pregnancy and the child. New York: Raven Press, 1982: 81-5
111. Acharya S, Bussel JB. Hematologic toxicity of sodium valproate. J Pediatr Hematol Oncol 2000; 22 (1): 62-5
112. Anderson GD, Lin YX, Berge C, et al. Absence of bleeding complications in patients undergoing cortical surgery while receiving valproate treatment. J Neurosurg 1997 Aug; 87 (2): 252-6
113. Kaaja E, Kaaja R, Matila R, et al. Enzyme-inducing antiepileptic drugs in pregnancy and the risk of bleeding in the neonate. Neurology 2002 Feb 26; 58 (4): 549-53
114. Pennell PB. Antiepileptic drug pharmacokinetics during pregnancy and lactation. Neurology 2003; 61 (6 Suppl. 2): S35-42

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