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Management of Epilepsy during Pregnancy

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Abstract

Managing epilepsy during pregnancy is to balance the maternal and fetal risks associated with uncontrolled seizures against the potential teratogenic effects of antiepileptic drugs (AEDs). A rational approach requires knowledge of such risks as well as an understanding of the effects of pregnancy on seizure control and of gestational effects on AED disposition. Uncontrolled tonic-clonic seizures are potentially hazardous to the mother and, although strict evidence is lacking, are generally also assumed to be more harmful to the fetus than are AEDs. However, infants who have been exposed to AEDs *in utero* run an increased risk of congenital malformations: approximately twice the rate reported in the general population. Earlier literature has largely failed to demonstrate differences in birth defect rates with different treatment regimens, which can be ascribed mainly to insufficient sample sizes. More recent data have indicated higher malformation rates with exposure to valproic acid compared with some other major AEDs. The teratogenic effects of valproic acid appear to be dose dependent, with higher risks at dosage levels >1000 mg/day. Polytherapy involving treatment with more than one AED also seems to be associated with an increased risk of birth defects compared with monotherapy. Recently, a few small-scale studies have investigated the possibility that exposure to AEDs *in utero* may adversely affect the postnatal cognitive development of the offspring. Some of these studies have

suggested that valproic acid poses a higher risk compared with other AEDs in this respect. These signals are important, but must be interpreted with caution because of the methodological shortcomings of the studies and because adequately powered prospective studies are necessary to draw firm conclusions. More reassuring findings have emerged regarding the obstetric outcome of pregnancy and the risk of worsening of epilepsy during pregnancy. In particular, it seems that the risk of obstetric complications is not significantly increased. Furthermore, most of the women with epilepsy have no change in their seizure frequency during pregnancy. The disposition of many AEDs may change during pregnancy, reflected in declining plasma drug concentrations. This seems to be most pronounced for lamotrigine and possibly also for oxcarbazepine, and can result in break-through seizures.

The common treatment strategy has been to use the appropriate AED for the woman's seizure disorder as monotherapy in the lowest effective dosage throughout pregnancy, the objective being to use AEDs in such a way that generalised tonic-clonic seizures are avoided but with minimised risks to the fetus, the newborn and the breast-fed infant. Valproic acid should be avoided if possible. Any major change in the treatment of a woman with epilepsy should ideally be completed before conception. Regular monitoring of drug concentrations is recommended during pregnancy, in particular for lamotrigine and oxcarbazepine.

Women with epilepsy are generally assumed to account for 0.3–0.4% of all pregnancies, although population-based studies suggest a prevalence of epilepsy among pregnant women of up to 0.7%.[1,2] The proportion of pregnancies with exposure to antiepileptic drugs (AEDs) is probably even higher, considering the widespread, and growing, use of AEDs for other indications than epilepsy.[3] Maternal epilepsy and AED treatment are associated with an increased risk for an abnormal pregnancy outcome compared with the general population. This complicates the management of epilepsy during pregnancy, which also needs to consider, among other things, fetal and maternal risks associated with uncontrolled seizures, the effect of pregnancy on seizure control, gestation-induced alterations in the disposition of AEDs, as well as the potential developmental toxicity of the treatment.

While, in general, focus in the literature has been on the teratogenic effects of AEDs, the proper management of women with epilepsy considering pregnancy requires that such risks are balanced against the potential hazards of uncontrolled epileptic seizures. The common strategy has been to use the appropriate AED for the woman's seizure disorder as monotherapy in the lowest effective dosage throughout pregnancy, the objective being to use AEDs in such a way that generalised tonic-clonic seizures are avoided but with minimised risks to the fetus, the newborn and the breast-fed infant. Most of the available information on risks associated with the treatment of epilepsy in pregnancy is related to the older generation AEDs, such as phenobarbitone (phenobarbital), phenytoin, carbamazepine and valproic acid. However, ten new AEDs have been introduced on the market since 1990 (felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin and zonisamide), some of which have become frequently used by women of child-bearing potential. These newer generation AEDs provide more treatment options but also new challenges for the management of epilepsy during pregnancy, since sufficient data for their rational use are often not yet available.

The objective of this article is to discuss the management of epilepsy during pregnancy based on a literature review of data, with emphasis on terato-

genic effects of AEDs as well as on seizure control during pregnancy and on effects of pregnancy on AED disposition.

A PubMed search was performed covering the period from 1966 to March 2007 by searching as text words at least one of the following terms: 'antiepileptic*', 'anti-epileptic*', 'anticonvuls*', 'anticonvuls*', 'epilep*', 'seizure*', 'barbit*, 'carbamazepine', 'ethosuximide', 'lamotrigine*', 'oxcarbazepine*', 'phenob*', 'phenytoin', 'diphenylhydantoin', 'dilantin', 'hydantoin', 'primidone*', 'valpro*', 'depak*', 'tiagabine*', 'topiramate*', 'felbamat*, 'trimethadione', 'vigabatrin' and 'levetiracetam'. Publications found were limited to those retrieved by searching as text word at least one of the following terms: 'pregnan', 'maternal', 'mother', 'parent*', 'fetal', 'fetal', 'fetus', 'fetus', 'feto*', 'foeto*', 'defects', 'embryopat', ('congenital' AND 'malformation*'), ('congenital' AND 'abnormalit*'), ('congenital' AND 'anomal*'), 'offspring*', 'utero', 'terato*', 'intrauterine', 'intra-uterine', ('before' AND 'birth'), 'infant', 'prenatal', 'prenatal', 'obstetric*, 'delivery' ('birth' AND 'outcome*') and ('children' AND 'of' AND 'women'). Eligible articles were further limited by excluding all the articles found by entering in the Medical Subject Headings field the expression ('animals' NOT 'human'). Additionally, a manual search was made of the authors' files, and colleagues with research experience in the field were approached to verify whether they were aware of any missing study. The list of references of the retrieved articles was examined for additional studies. We also examined reference lists of reviews and retrieved reports.

1. Hazards Associated with Uncontrolled Seizures

Seizures may be harmful, causing physical injuries and occasionally even death of the patient with epilepsy. This is of course one of the reasons for treating people with epilepsy in general,[4] and these concerns related to maternal health are equally relevant during pregnancy. In fact, women with epilepsy accounted for 3.8% of all maternal deaths in the UK during 1985–99,[5] considerably more than expected from the prevalence of epilepsy in pregnancy. The mortality was partly related to seizure occurrence after stopping AED treatment.[5] Although the absolute risk is very low, the data underline the importance of seizure control for maternal health.

The fetal effects will depend on the type of seizures. Seizures other than generalised tonic-clonic seizures are unlikely to cause fetal harm. However, convulsive seizures induce lactic acidosis,[6] which is transferred to the fetus.[7] Convulsive seizures may also cause fetal bradycardia[8] and status epilepticus can result in intrauterine death.[9,10] However, the prospective EURAP antiepileptic drugs and pregnancy registry reported only one case of intrauterine death[10] and no maternal mortality among 36 cases with status epilepticus (12 of which were convulsive). Furthermore, recent data suggest that the number of stillbirths is not increased among women who are adequately treated for their epilepsy during pregnancy.[11,12]

2. Effect of Pregnancy on the Course of Epilepsy

The influence of pregnancy on the course of epilepsy varies: seizure frequency may increase, decrease or remain unchanged. On this point, literature data are somewhat contradictory: in most cases no major changes in seizure frequency are seen in pregnancy (the proportion ranging from 4–96% in the publications), while in 4–75% of the cases seizures become more frequent during pregnancy; the reverse may be true in other cases (0–82%).[10,13-33] The effect of pregnancy may vary from patient to patient and in different pregnancies of the same patient.[13,31] However, most population-based studies indicate that seizure frequency remains unchanged during pregnancy in the majority of patients, whereas deterioration and improvement is seen in similar proportions.[14,16,31,34] The largest prospective study published so far (EURAP), based on 1736 pregnancies, concluded that 58% remained seizure free throughout pregnancy and that 18% had convulsive seizures on some occasion during pregnancy.[10]

Some studies report that changes in seizure control occur predominantly during the first and third trimester, whereas seizure frequency tends to revert to pre-pregnancy values after delivery.[14,17,19,23,31] Others reported a trend towards improvement during the first trimester with no further changes in the second and third trimester.[16]

Pharmacokinetic, metabolic, hormonal, physiological and psychological factors have all been suggested to be involved as contributing causes to gestational changes in seizure control. In some cases, changes in seizure frequency may be related to lack of compliance[15,19] or for other reasons resulting in decreased plasma AED concentrations.[15,19,35,36] However, changes in seizure frequency are often unrelated to plasma AED concentrations.[15,16,18,26,28,37] A more detailed discussion on this possible relationship is provided in section 3.

Epilepsy-related factors potentially explaining worsening of seizures during pregnancy include localisation-related epilepsy,[10,15,16,28,38] and epilepsy severity, expressed as illness duration[14,16,17,24,28,29,31] or poor control before pregnancy.[28,31] A protective effect of good control before pregnancy has been signalled by two studies.[17,24] The deterioration of seizure control has also been attributed to stress, lack of sleep and fatigue,[19,22] or an increased estrogen/progesterone ratio.[21,23]

Although the data on general changes in seizure control during pregnancy are conflicting, the findings are consistent concerning an increased risk of seizures during labour and delivery. On average, seizures occur at labour and during delivery in 2.5% of the patients,[10,12,14,15,25,28] with a higher risk for patients who experienced seizures earlier during pregnancy.[10]

Status epilepticus occurs in about 1% of the patients,[10,14-19,24,25,28,31,37,39] but slightly more often, 1.8%, in the EURAP cohort, where non-convulsive status epilepticus was also included.[10]

3. Effects of Pregnancy on Antiepileptic Drug Disposition and Response

Maternal plasma AED concentrations are important as they are related to the antiepileptic effects in the treated woman as well as reflecting the drug exposure to the fetus. Older generation AEDs[40-42] as well as newer AEDs[43-52] cross the placenta and distribute into fetal tissue. Human data demonstrate that in early pregnancy – during the stage of organogenesis – considerable amounts of phenytoin,[53] primidone, phenobarbitone[54,55] and carbamazepine,[56] as well as some of their metabolites,[40] are present in fetal tissues, and that potentially reactive metabolites of anticonvulsants can be formed by the fetal liver and accumulate in some organs.[40] As far as we know, no data are available on placental transfer in early pregnancy for the newer AEDs. Although, fetal-maternal drug concentration ratios are affected by several factors (e.g. the rate of placental transfer in both directions, placental drug metabolism, differences in maternal and fetal protein binding), it is reasonable to assume that fetal exposure could be derived indirectly from maternal plasma concentrations. Furthermore, although there is insufficient evidence to demonstrate a relationship between the extent of fetal exposure to AEDs and the teratogenic risk, high maternal concentrations must be considered as possibly harmful for the fetus.

Pregnancy is associated with several physiological changes – such as impaired gastrointestinal absorption, increased volume of distribution, decreased protein binding and changes in drug metabolising capacity – that may affect drug disposition and thus maternal plasma concentrations and fetal exposure.[57,58] As a result of these changes, total plasma concentrations of most AEDs tend to decrease, even if there is a wide variability in the degree and the time course of such a decrease.[59] Free drug concentrations also tend to decrease, but to a lesser extent than total concentrations. Because only unbound concentrations are pharmacologically active, total plasma concentrations can be misleading for highly protein-bound AEDs such as phenytoin and valproic acid.[60,61]

The decline of AED concentrations generally begins during the first trimester. In late pregnancy, the decrease is on average: 55–61% for phenytoin total and 18–31% for unbound concentrations;[60,62-65] 0–42% for carbamazepine total and 0–28% for unbound concentrations;[16,60,64,66-68] 50–55% for phenobarbitone;[61,69] 55% for primidone; 70% for primidone-derived phenobarbitone;[69,70] and 50% for valproic acid total and 0–29% for unbound concentrations (at the end of pregnancy valproic acid unbound concentrations may even be slightly higher than those of pre-pregnancy).[60,71]

Lamotrigine is the most extensively investigated of the newer AEDs. Pharmacokinetic changes are pronounced: on average, plasma lamotrigine concentrations decreased by 68% during pregnancy, with a wide interindividual variability and sometimes with deterioration of seizure control.[72-76] The decrease of plasma lamotrigine concentrations is markedly reduced[77] when lamotrigine is taken in combination with valproic acid.

More limited data indicate a decrease of a similar magnitude for the active moiety of oxcarbazepine, its monohydroxy derivative.[78,79] A less pronounced, but still marked, decrease in levetiracetam concentrations has been reported in two small studies.[80-82] Very limited or no information is available on possible changes in disposition of the other newer generation AEDs (e.g. gabapentin, vigabatrin, pregabalin, tiagabine, topiramate and zonisamide).[59]

Most earlier studies involving older generation AEDs have failed to demonstrate a relationship between seizure control and alterations in plasma AED concentrations.[16,18,26] However, with lamotrigine monotherapy, break-through seizures have been associated with the marked decline in plasma concentrations in a relatively high proportion of patients (45–75%).[75,76] Prospective pregnancy register data also indicate that patients receiving lamotrigine more often need dosage adjustments during pregnancy[10,83] or additional AEDs.[10] Moreover, in a report from the Australian Epilepsy and Pregnancy Register, control of convulsive seizure was significantly worse for lamotrigine than for valproic acid (during the entire pregnancy) and for carbamazepine (during the second and the third trimester).[83] However, the lack of information on plasma concentrations and on seizure frequency changes during pregnancy make it impossible to attribute these finding to the decline of plasma lamotrigine concentrations documented by previous studies.[73-76,84]

Oxcarbazepine is the only other AED reported to be associated with a poorer seizure control during pregnancy than other monotherapies. The EURAP registry reported that about 60% of the total 1956 enrolled pregnancies[10] were seizure free, and found that partial epilepsy, polytherapy and oxcarbazepine in monotherapy were independently associated with an increased seizure frequency in the second and third trimester compared with the first trimester.[10] This could also be explained by pharmacokinetic alterations, since the pronounced decline in plasma concentrations of the active moiety of oxcarbazepine was associated with break-through seizures in a small case series.[78]

4. Risk of Malformations

4.1 Methodological Issues

The incidence of malformations in the offspring of epileptic women is two to three times higher than in the general population,[85] although reported malformation rates vary between studies. The reason for the increased risk is considered to be multifactorial and not only due to teratogenic effects of AEDs. Several studies have reported an increased risk of malformations in the offspring of untreated mothers or of fathers with epilepsy, suggesting that epilepsy *per se* may increase the risk of birth defects.[86-93] However, a recent meta-analysis[94] suggested that the malformation rate among the offspring of women with untreated epilepsy was similar to that of non-epileptic controls, although these results should be interpreted with caution because of differences in ascertaining cases and controls, and the small numbers of studies and cases considered.

The conflicting results partly reflect methodological differences. The populations studied vary con-

siderably. Some papers included only women with active epilepsy or with epilepsy and pharmacological treatment, others also included women not taking AEDs or on AEDs for other reasons than epilepsy. Researchers also adopted different exclusion criteria, such as maternal malformations, chronic or genetic diseases, and twins or multiple pregnancies of the same patient.

Other relevant factors for variations in outcome are differences in the timing of outcome assessment and in the selected teratogenic endpoint. Many birth defects are not detectable at birth, while others may disappear later in life. This is illustrated in table I, which summarises results from 113 studies that differed in time of assessment and in teratogenic endpoint. Of the 113 studies, 83 had major malformations as the endpoint and 69 of those relied on assessment at birth only.[2,21,27,28,31,84,95-157] In 14 studies, the assessment was extended to later in life.[83,86,93,109,158-167] In 30 studies, minor anomalies were also included in the assessment; of these, 20 restricted the examination of the children to the time of birth,[12,25,87,90,168-183] and 10 also assessed the children at later stages.[89,146,184-191]

Assessment only at birth will underestimate the risk of adverse fetal outcome: the prevalence of malformations is reduced by about 40% when the follow-up ends at birth compared with an extended follow-up of the children (table I). Also, as expected, on average the rate is lower when the endpoint is limited to major malformations.

A major limitation of most previous studies of teratogenic effects of AEDs is the small number of enrolled exposed pregnancies, and thus their low statistical power. For this reason, major efforts have been made in recent years to establish large-scale prospective AEDs and pregnancy registries.[83,112,138,156,192] These national and international registries have each been successful in enrolling thousands of pregnancies with exposure to AEDs. Some have also already published data on teratogenic outcome with different AEDs.[83,112,138,156] However, many of the methodological issues discussed in this section are also relevant for these registries, as they differ with respect to populations at study, methods for enrolment, inclusion and exclusion criteria, criteria for classification of teratogenic outcome, as well as duration of follow-up of the offspring.[193] Higher malformation rates in the Australian register[193] and in EURAP[193] could be explained by the extended follow-up of the infants until 1 year after birth. Exclusion of pregnancies with abnormalities detected by prenatal testing before enrolment might contribute to lower rates of birth defects in the UK register. Direct comparisons of malformation rates between the registries are therefore complicated.

4.2 General Overview

Despite the problems in the interpretation of the available studies on teratogenic risks, some observations are firmly established.

Firstly, maternal epilepsy is associated with a 2- to 3-fold increase in the risk of birth defects. Table II summarises the results of 26 controlled studies dealing with major malformations in pregnancies of women with treated as well as untreated epilepsy, subdivided according to the time of malformation assessment.

Secondly, the increased risk is primarily associated with pharmacological treatment (table II). Irrespective of the time of assessment of the offspring, malformation rates were 2–3 times higher among the total of 4630 offspring exposed to AEDs

Table I. Rates of adverse pregnancy outcome in pregnancies from 113 studies by type of adverse outcome (major malformations vs major malformations and minor anomalies combined) and by time of assessment of outcome (at birth vs later in life)

Teratogenic endpoint	Birth		Paediatric age		Grand total	
	total outcomes	no. (%)	total outcomes	no. (%)	total outcomes	no. (%)
Major malformations	18 369	841 (4.6)	2557	199 (7.8)	20 926	1040 (5.0)
Major malformations and minor anomalies	10 617	602 (5.7)	2259	240 (10.6)	12 876	842 (6.5)
Grand total	28 986	1443 (5.0)	4816	439 (9.1)	33 802	1882 (5.6)

Table II. Rates of congenital malformations in pregnancies from 26 studies by time of assessment of outcome in pregnancies in women with treated epilepsy, untreated epilepsy and in control pregnancies of untreated women without epilepsy

Time of examination	Offspring of treated mothers with epilepsy		Offspring of untreated mothers with epilepsy		Offspring of mothers without epilepsy	
	total outcomes	no. (%)	total outcomes	no. (%)	total outcomes	no. (%)
Birth[a]	4102	240 (5.9)	1149	31 (2.7)	1 863 263	40 184 (2.2)
Paediatric age[b]	528	44 (8.3)	143	5 (3.5)	1 075	37 (3.4)
Grand total	4630	284 (6.1)	1292	36 (2.8)	1 864 338	40 221 (2.2)

a References.[2,27,31,95,103,107-110,115,117-119,121,125,130,140,142,149-151,153]

b References.[93,158,160,166]

compared with those of untreated mothers with epilepsy or of mothers without epilepsy (table II).

Thirdly, the risk of malformations increases when there is a positive family history of malformations, as suggested by cohort[32,101,105,121,141,152,158,182,184,194-199] and family[200-210] studies. Genetic susceptibility to teratogenic effects of AEDs is also suggested by case-control studies reporting a higher proportion of relatives with epilepsy in patients with cleft palate or lip,[211-215] or neural tube defects.[216,217] One study[218] found extensive use of phenobarbitone among 414 children with cleft palate or lip. However, the statistical significance disappeared after exclusion of cases with a positive family history of malformations.

A further relatively well documented observation is that the occurrence of seizures during the first trimester does not increase the risk of malformations.[2,12,27,32,84,86,90,93,109,118,151,152,157,158,166,187,197] Only a few studies have observed an association between seizures and malformations.[87,128,142,189,197]

Valproic acid is the only drug for which several studies observed a dose-related risk of birth defects.[32,104,146,147,164,168,219,220] However, there are studies that have failed to find differences in maternal valproic acid dosages between malformed and healthy babies.[84,118,156] Recently, a dose-related effect was also reported by the UK registry for lamotrigine.[138]

The severity of epilepsy may confound the association between dosages and the risk of malformations, as well as the association between polytherapy and the risk of malformations. It is a commonly held opinion that polytherapy with AEDs is associated with higher malformation rates than monotherapy. This is indeed supported by the majority of studies but the data are not completely consistent. Table III summarises the results of 74 studies that included pregnancies of women who were exposed to either monotherapy or polytherapy. Studies that included only major malformations identified at birth reported lower malformation rates among children of mothers treated with AEDs on monotherapy compared with those exposed to polytherapy. Studies on major malformations with longer follow-up and studies also including minor anomalies on average reported similar rates in the two groups. The interpretation of outcomes with polytherapy is further complicated because polytherapy comprises numerous different mostly unspecified AED combinations. Combinations of different AEDs are likely to differ in their teratogenic potential. Malformation rates in studies of polytherapy will therefore vary depending on the types of AED combinations that are included.

The types of malformations reported at higher rates in the offspring of epileptic mothers are heart defects, neural tube defects, facial clefts, hypospadias and limb reduction defects. There is fairly solid evidence suggesting a specific association between neural tube defects and valproic acid[101,147,216,221-226] and, to a lesser extent, between barbiturates and heart defects.[27,101,197,222,224,227] Some studies also reported a higher risk of limb reduction defects associated with valproic acid exposure[222,228] or hypospadias,[147,222] and a higher risk of oral cleft with barbiturates.[197,222,224] However, these associations need to be confirmed.

4.3 Malformations by Specific Drugs

This overview of malformations by specific AEDs focuses on exposure as monotherapy.

4.3.1 Older Generation Antiepileptic Drugs

Carbamazepine

From 1987 to 2006, 13 studies analysed the risk of malformations in the offspring of women exposed to carbamazepine in monotherapy compared with different types of reference populations.[2,32,83,99,101,138,140,146,147,162,165,168,181,183-185] Two of those found that carbamazepine was associated with an increased risk of malformation compared with the AED with the lowest malformation rate in the same study[146] or with healthy controls.[147] The first study re-analysed the data of five European prospective studies.[146] Using the data of all centres, the authors found 22 malformations in 280 children exposed to carbamazepine; the malformation prevalence of each AED in monotherapy was compared with that of phenytoin. The crude overall analysis showed no significant difference among different AEDs in monotherapy; whereas after adjustment for potential confounders, exposure to carbamazepine was significantly associated with an increased risk of malformations (relative risk [RR] 2.8; 95% CI 1.1, 7.3). Similar results were also observed for valproic acid and phenobarbitone monotherapy. The analysis limited to the two centres that included matched unexposed controls showed a significant increased risk of malformations only for carbamazepine (RR 4.9; 95% CI 1.3, 18.0) and valproic acid.[146] The second study retrospectively compared a group of children of epileptic women with non-epilepsy controls.[147] Carbamazepine and valproic acid reached statistical significance, while phenobarbitone and phenytoin did not; the RR for carbamazepine (n = 376) was 2.6 (95% CI 1.4, 5.0).

However, 11 of the 13 studies did not find an increased risk of malformation for carbamazepine compared with no AED exposure,[32,83,168,184] other AED monotherapies,[99,138,183] other potential teratogens[162] or healthy controls.[2,140,181] The teratology service in San Diego, CA, USA, published the results of a study that included only exposures to carbamazepine; no differences in malformation rates were found between 39 children exposed to carbamazepine as monotherapy (6.7%) and 70 children exposed to other potential teratogens (7.1%).[162] Six additional studies reported significantly fewer malformations for carbamazepine than for one or more other AEDs as monotherapy.[138] In particular, the UK registry,[138] the largest prospective study published to date, reported 20 malformations among 927 carbamazepine pregnancies. This corresponds to a rate of 2.2%, which was even lower, although not significantly, than the 3.3% observed for no AED exposure (8 of 239). Three other studies compared the outcome of the offspring of women exposed to carbamazepine as monotherapy with that of children of epileptic women on no AEDs.[32,83,168] The rates of malformation in the carbamazepine group and in the reference population were 2.7% (n = 805) versus 2.8% (n = 939),[168]

Table III. Rates of adverse pregnancy outcome in pregnancies from 74 studies by type of adverse outcome (major malformations vs major malformations and minor anomalies combined), by time of assessment of outcome (at birth vs later) and by type of antiepileptic drug exposure (monotherapy vs polytherapy)

Teratogenic endpoint	Birth		Paediatric age	
	monotherapy total no. of outcomes (% pathological outcomes)	polytherapy total no. of outcomes (% pathological outcomes)	monotherapy total no. of outcomes (% pathological outcomes)	polytherapy total no. of outcomes (% pathological outcomes)
Major malformations[a,b]	8 339 (4.0)	4253 (6.8)	911 (7.0)	515 (6.6)
Major malformations and minor anomalies[b,c]	3 032 (9.4)	593 (8.6)	784 (11.1)	1026 (11.5)
Grand total	11 371 (4.3)	4846 (7.0)	1695 (8.9)	1541 (9.9)

a References.[2,21,27,28,31,84,96-98,101-103,106-109,114,115,117-120,122,124-128,130,132-138,141-143,146,147,149,152,154,155]

b References.[83,93,158-160,162-164,166,167]

c References.[12,168,172,174,175,177,181,183]

3.9% (n = 155) versus 2.5% (n = 40)[83] and 5.7% (n = 158) versus 3.1% (n = 97).[32] In a large Swedish population-based cohort,[183] the pregnancy outcome of each AED in monotherapy was compared with each of the other AED monotherapy exposures. Similar or lower rates were reported for the 703 children of women exposed to carbamazepine than for those whose mothers were taking lamotrigine (n = 90), phenytoin (n = 103) or valproic acid (n = 268). Similar findings were reported by Waters et al.[181] who studied 33 children of women treated with carbamazepine as monotherapy, 21 of women treated with phenobarbitone and 28 with phenytoin.

Finally, in four other studies, with respect to malformation rates, none of the AEDs evaluated (one of which was carbamazepine) reached statistical significance compared with other AED monotherapies,[99] matched controls[2,140] or no AED exposure.[184] These studies included offspring exposed to monotherapy with phenobarbitone,[2,99,184] phenytoin[2,99,140,184] and valproic acid.[184]

Phenobarbitone

Recently, the North American Registry reported five malformations among 77 children exposed to phenobarbitone monotherapy (6.5%);[112] four were heart malformation. Compared with the background rate – an external control population (1.6%) – the risk was significantly increased (RR 4.2; 95% CI 1.5, 9.4). Compared with other unspecified monotherapy exposures from the same registry, the difference was not statistically significant (23 of 796; 2.9%).

The teratogenicity of phenobarbitone as monotherapy was evaluated by eight other studies,[2,28,32,99,101,146,147,181,184] of which two reported significantly more malformations for phenobarbitone than for phenytoin (RR 4.2; 95% CI 1.0, 18.6)[146] or for healthy controls.[181] The latest study[181] analysed abnormal outcomes in terms of death and congenital anomalies in a prospective cohort of 130 offspring of epileptic mothers (82 on monotherapy); the AEDs mostly used in monotherapy were phenobarbitone, phenytoin and carbamazepine. Phenobarbitone monotherapy was the only AED significantly associated with abnormal outcomes (5 of 21) compared with controls.

These finding were not confirmed by the other six studies that failed to find a correlation between the occurrence of malformation and the exposure to phenobarbitone compared with no AED exposure,[184] other AED monotherapies[99,101] or healthy controls.[2,28,147]

Primidone

Few studies have investigated the effect of prenatal exposure to primidone monotherapy compared with other monotherapies,[99] no AED exposure,[32] phenytoin (the AED associated to the lowest malformation rate)[146] or healthy controls,[147] and only one found that the drug was associated with an increased risk of malformations. The prevalence of malformation among the offspring of the Canadian, Japanese and Italian prospective cohorts was 14.5% (n = 35) as compared with 3.1% with no AEDs exposure (n = 97).[32] The authors reported an increased risk also for valproic acid but not for the other AEDs.

Phenytoin

Publications that evaluated the occurrence of malformations among the offspring of women exposed to phenytoin monotherapy were published from 1987 to 2006. None of them reported a significant increased risk compared with no AED exposure,[32,168,184] other AED monotherapies[99,101,138,146,165,183] or healthy controls.[2,140,147,181]

Valproic Acid

Twelve studies, published from 1987 to 2006, analysed the risk of malformations for the offspring of women receiving valproic acid as monotherapy, compared with several types of reference populations.[32,99,138,143,146,147,156,165,168,183,184]

Three recent studies found a greater risk only for valproic acid compared with no drug exposure. In the first study,[168] the odds ratio (OR) for valproic acid (n = 263) versus no AEDs (n = 939) was 4.18 (95% CI 2.31, 7.57), and in the second study[165] the RRs were 3.0 (95% CI 1.22, 7.92) versus carbamazepine (n = 110), 27.1 (95% CI 5.12, 502.00) versus lamotrigine (n = 98) and 2.7 (95% CI 0.92, 8.94) versus phenytoin (n = 56). However, it should be

noted that when lamotrigine was removed from the analysis, carbamazepine, phenytoin and valproic acid did not differ in a three-group internal comparison.[165] The third study, the North American registry, published the data concerning valproic acid separately: the authors compared valproic acid with all other monotherapies and found significantly more malformations with valproic acid (10.7% of 149 subjects vs 2.9% of 1048).[156] Unfortunately, no information is available on the type of AEDs used as reference population.[156]

Three studies reported that valproic acid was one of the AEDs for which there was a statistically significant increased risk.[146,147] The first, the joint analysis of Canadian, Japanese and Italian prospective cohorts,[32] found no differences across different monotherapy regimens but a significant increase for primidone (see section on primidone) and valproic acid (9 of 81; 11.1%) compared with no AED exposure. The other two studies found an increased risk only for carbamazepine, valproic acid[146,147] and phenobarbitone,[146] and, in one study,[147] only after adjustment for potential confounders. The RRs were 4.1 (95% CI 1.9, 8.8) versus healthy controls[147] and 3.7 (95% CI 1.2, 11.8) versus the drug with the lowest malformation rate (phenytoin).[146] The RR for valproic acid versus healthy controls was 4.9 (95% CI 1.6, 15.0) when the analysis was restricted to two of the five centres.[146]

Different findings were reported by two studies that found a higher risk for valproic acid compared with carbamazepine. In the first, a large historical cohort,[183] the OR calculated for valproic acid (n = 268) versus carbamazepine was 2.51 (95% CI 1.43, 4.68); in the second, the UK registry,[138] the adjusted OR was 2.97 (95% CI 1.65, 5.35). The authors also reported an increased risk for valproic acid than for lamotrigine, but the significance was lost in the multivariable analysis.

The remaining three studies failed to find an increased risk for valproic acid monotherapy versus no AED exposure[184] or other AED in monotherapy.[99,225]

4.3.2 Newer Generation Antiepileptic Drugs

Information on the teratogenic risk of new generation AEDs is scanty and lamotrigine is the only drug for which a reasonable amount of data are available. Four studies[83,138,165,183] analysed the risk associated with lamotrigine monotherapy. The prevalence of malformations ranged from 0%[83] to 4.4%.[183]

Additional information on lamotrigine can be drawn from the manufacturer's prospective registry,[102] which reported congenital malformation in 2.9% of 414 offspring of women exposed to lamotrigine in monotherapy. The rate of malformations among 88 lamotrigine and valproate combination exposures was 12.5% compared with 2.7% in 182 exposures to lamotrigine in combination with antiepileptic drugs other than valproic acid.[102]

A multicentre study carried out in Argentina[134] found that only one of the 55 infants exposed to oxcarbazepine (35 on monotherapy) was born with a malformation. A retrospective population-based study from Finland[168] reported similar findings, i.e. only one malformed outcome among the 99 live births exposed to oxcarbazepine monotherapy. An overall malformation rate of 2.4% among 248 exposures to monotherapy and of 6.6% among 61 exposures to polytherapy was recently reported in a review of all published cases, also including the Argentinean cases and some of the Finnish cases.[229] The only available data on the other new AEDs are those of the UK registry:[138] among pregnancies exposed to monotherapy, two malformations were reported in 28 pregnancies exposed to topiramate, one of 31 exposed to gabapentin and none among 39 levetiracetam monotherapy exposures.[230]

5. Developmental Delay

Studies on long-term outcomes after prenatal exposure to AEDs have reached conflicting conclusions. Some of them report normal intelligence[163,231-234] or a transient developmental delay in comparison with children of healthy controls[80,86,235-238] or to children of fathers with epilepsy.[239] According to others, children of mothers with epilepsy have a greater risk of permanent develop-

mental delay.[87,188,191,240-242] Others again describe specific cognitive deficits unrelated to mental deficiency.[186,191,195,233,234,243-254]

Regarding long-term adverse outcomes in relation to exposure to individual AEDs, in recent years a great deal of attention has been paid to valproic acid. Several studies reported specific cognitive deficits in children born to mothers taking valproic acid during pregnancy,[242,243,249,252,255-257] but these studies are characterised by important methodological shortcomings.[5] Other AEDs reported to be associated with adverse cognitive outcomes are phenytoin,[240,241,246,253] phenobarbitone,[191] carbamazepine[162,195] and primidone.[252]

Studies of cognitive development have specific methodological problems. Longitudinal studies are lacking and most of the so-called prospective studies are characterised by a low response rate and have collected only maternal data prospectively, since children were identified years after birth. The risk of bias is higher than that for studies on congenital malformations. A multitude of factors can affect cognitive development and a number of risk factors are known to be relevant in the general population. Such factors may be prenatal (such as low parental intelligence level or socioeconomic status, or family history of developmental disorders), perinatal (prematurity, low birthweight or low Apgar scores) or postnatal (co-morbidities or adverse environmental factors). Each of these factors may independently cause impairment of psychomotor development. None of the published studies on AEDs has taken into account all these factors. In addition, most of them have failed to control for epilepsy-related factors such as severity of the disease, and the possible consequences on the mother's ability to care for the child, and of the maternal side effects of AEDs. For example, the findings of two recent studies suggested that the assumed association between valproic acid and cognitive deficits may depend, at least in part, on a higher rate of valproate-exposed mothers with low education levels.[249,256]

Another main point is that pathological and normal outcomes are often confused because of differences in endpoints across the studies (frequency of mental impairment, global or partial IQs). Partial IQ scores significantly reduced compared with controls are often presented as a signal of the increased risk of mental impairment, despite the fact that they are within the expected age standardised average range for the general population.

Considering these methodological problems, and the inconsistencies in published results, it must be concluded that to date there is no definitive evidence that long-term adverse outcomes in children of epileptic mothers can be ascribed to AEDs. There are signals concerning valproic acid and verbal IQ, and these need to be confirmed or refuted in prospective, adequately controlled and powered studies.

6. Folate Supplementation

Low maternal levels of folate and vitamin B_1, and high levels of homocysteine have been associated with an increased risk of neural tube defects in the general population.[258-261] Furthermore, periconceptional folate supplementation has been shown to reduce the risk of birth defects significantly and in particular that of neural tube defects in the general population.[262-264] In women with epilepsy, low folate levels have been reported consistently during pregnancies of women treated with AEDs.[265] Some studies have also reported an increased risk of adverse pregnancy outcome with decreasing folate levels in women on AEDs.[178,266,267]

However, evidence is still lacking for the effectiveness of folic acid in the prevention of AED-induced teratogenicity, and the appropriate supplementation dosage is still debated.[268] Nevertheless, periconceptional supplementation with folic acid is usually recommended for women exposed to AEDs,[268-270] but the women need to be informed about the lack of solid evidence documenting the efficacy. Suggested dosages range from 0.4 to 5 mg/day.

7. Breast Feeding

The amount of AEDs that the infant will be exposed to through breast feeding depends on the maternal plasma concentration, the extent of transfer

to breast milk and the amount of milk intake by the infant, plus the infant's absorption, distribution, metabolism and elimination of the drug. Low milk-maternal plasma concentration ratios and low plasma concentrations in suckling infants have been documented with phenytoin[40] and valproate,[271] and in general also for carbamazepine.[272] Drug transfer to breast milk appears to be more extensive for ethosuximide[41] and phenobarbitone,[273] and the risk for accumulation in the suckling infant has been discussed in the literature in particular for phenobarbitone. For lamotrigine, the milk-maternal plasma concentration ratio has been <1.0, but lamotrigine levels as high as 11 μmol/L have been reported in suckling infants.[72] The levetiracetam milk-maternal plasma concentration ratio is close to unity but plasma concentrations in the nursed infants are generally low.[82,274] The published data are more limited for other newer generation AEDs. The mean topiramate milk-maternal plasma concentration ratio was 0.86 in five mothers receiving treatment with topiramate, and drug concentrations in the nursed infants were very low (below the level of quantification) 2–3 weeks after delivery.[50] Preliminary data from five mothers treated with gabapentin demonstrate a similarly extensive transfer to breast milk, with a mean milk-plasma concentration ratio of 1.0 and very low gabapentin levels in the suckling infants 2–3 weeks after birth.[52] There is only one published case with breast milk data on oxcarbazepine, reporting a milk-plasma ratio of 0.5 for the active monohydroxy derivative but no information on serum concentrations in the infant.[48] Information on zonisamide is also limited to a single case with a milk-plasma concentration ratio of 0.9 and no data on drug concentrations in the nursed infant.[275] To our knowledge, there are no published reports on breast feeding under treatment with tiagabine or pregabalin.

While the numbers on some of the newer AEDs, in particular, are small, it is worth noting that no adverse effects related to breast feeding have been reported with these drugs. In general, breast feeding is thus encouraged,[269] although considerable drug concentrations have been reported occasionally in children of mothers treated with some AEDs, such as phenobarbitone, ethosuximide and lamotrigine. Mothers using these AEDs should be informed of the possibility of drug effects on the neonate but not generally advised against breast feeding.[276]

8. Discussion and Conclusions

How can the present state of knowledge be translated into practical management of epilepsy during pregnancy? It should be acknowledged that we are still missing much essential information and current management is based partly on assumptions.

The first assumption is that generalised tonic-clonic seizures are more harmful to the fetus as well as to the mother than are AEDs. This assumption is generally accepted in treatment guidelines,[85] although our understanding of the fetal risks in association with seizures is less than satisfactory. From this assumption it follows that AEDs are indicated during pregnancy if such treatment is considered necessary to control tonic-clonic seizures. With respect to fetal hazards, a distinction is made between tonic-clonic and other seizure types. However, for the mother, uncontrolled seizures of other types, e.g. complex partial seizures, may well be incapacitating and also constitute an indication for treatment during pregnancy. Furthermore, if uncontrolled, such seizures may generalise and thus potentially cause fetal harm. Such risks have to be assessed individually.

On the basis of the observations suggesting that polytherapy is associated with greater risks for adverse pregnancy outcome, AEDs should be prescribed in monotherapy whenever possible. Another assumption is that teratogenic risks are dose related, which is a reasonable assumption, although the supportive clinical evidence is limited to valproic acid teratogenicity. However, from this, it follows that the AED should be prescribed at the lowest effective dosage.

The overwhelming evidence for AED developmental toxicity relates to structural malformations, for which organogenesis in early pregnancy is the critical period. Hence, to be effective in reducing fetal risks, changes in therapy should be accom-

plished before conception. This is also important in order to avoid unnecessary seizure-related risks to the fetus, should treatment adjustments result in seizures. Pregnancies should thus ideally be planned and treatment reviewed perhaps a year before conception to allow for a gradual change in treatment and an assessment of the effectiveness of the new treatment. This pre-pregnancy review may include the following: (i) a discussion on gradual withdrawal of treatment in patients who have been seizure-free for some years; this has to be based on an individual evaluation of the risk of relapse on withdrawal and its consequences; (ii) simplification of a polytherapy to monotherapy; (iii) titration of dosage to establish lowest effective level; and (iv) change of AEDs to the most appropriate agents with respect to teratogenic risks as well as seizure control.

Unfortunately, clinical studies, including the pregnancy registries, have not provided us with evidence of a non-teratogenic AED or an AED superior to all others regarding lack of developmental toxicity. However, independent studies have suggested a greater risk for malformations associated with valproic acid compared with other AEDs. Hence, if possible, valproic acid should be avoided in women planning pregnancy. However, there are women, e.g. some with juvenile myoclonic epilepsy, where a drug switch will fail and where seizure control can be maintained only with valproic acid. For those, it should be noted that a low dose of valproic acid (<800–1000 mg/day) may not be more harmful than other AEDs.[83]

Once the lowest effective dosage of an AED has been established before pregnancy, it is advisable to determine its plasma concentration. This concentration can be used as the individual reference concentration when drug concentrations are measured during pregnancy. The frequency by which AED concentrations should be monitored varies but once each trimester is often recommended. However, more frequent sampling is recommended for lamotrigine and oxcarbazepine, as the decline in plasma concentrations of these drugs can be pronounced and associated with break-through seizures. If phenytoin and valproic acid are being monitored, measuring unbound concentrations is recommended.

Pre-pregnancy counselling should include information about risks with seizures as well as teratogenic risks with AEDs. Patients should also be informed of the possibilities and limitations with prenatal screening for birth defects, and such screening should be offered as appropriate for the specific risks and the individual setting. Information on folic acid supplementation should also be provided in pre-pregnancy counselling.

Finally, it should be emphasised that while this review has focused on risks, the vast majority of women with epilepsy will have uneventful pregnancies and give birth to perfectly healthy children.

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