Antiepileptic Treatment in Pregnant Women: Morphological and Behavioural Effects

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Abstract It is well established that children exposed to antiepileptic drugs (AEDs) in utero have an increased risk of adverse pregnancy outcomes including foetal growth retardation, major congenital malformations and impaired postnatal cognitive development. However, due to the significant maternal and foetal risks associated with uncontrolled epileptic seizures, AED treatment is generally maintained during pregnancy in the majority of women with active epilepsy.

The prevalence of major malformations in children exposed to AEDs has ranged from 4 to 10%, 2–4 times higher than in the general population. More recent studies

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H.W. Seyberth et al. (eds.), *Pediatric Clinical Pharmacology*,
Handbook of Experimental Pharmacology 205,
DOI 10.1007/978-3-642-20195-0_15,

suggest a smaller increase in malformation rates. Malformation rates have consistently been higher in association with exposure to valproate than with carbamazepine and lamotrigine. Some prospective cohort studies also indicate reduced cognitive outcome in children exposed to valproate compared to carbamazepine and possibly lamotrigine. Information on pregnancy outcomes with newer generation AEDs other than lamotrigine are still insufficient.

Keywords Antiepileptic drugs • Teratogenicity • Congenital malformations • Pregnancy • Epilepsy

1 Introduction

The first report on possible human teratogenic effects of antiepileptic drugs (AEDs) was published more than 40 years ago (Meadows 1968). Meadows reported six children with orofacial clefts, some with additional abnormalities of the heart and face, all of whom had been exposed to AEDs in utero. Treatment was mainly different combinations of phenobarbital, phenytoin and primidone. In a subsequent retrospective survey of more than 400 pregnancies with epilepsy Speidel and Meadow (Speidel and Meadow 1972) found a twofold increase in malformation rate among children of mothers with epilepsy exposed to AEDs. A specific association between trimethadione and a very high prevalence of malformations was also reported early (German et al. 1970). Since then numerous studies with different methodologies have reported increased rates of teratogenic outcomes in mothers with epilepsy (Harden et al. 2009; Meador et al. 2008; Tomson and Battino 2005; Tomson and Hiilesmaa 2007). These adverse outcomes include major congenital malformations, minor anomalies and dysmorphism, growth retardation, and impaired cognitive development. In addition to trimethadione, all of the major old generation AEDs such as phenobarbital, phenytoin, valproate and carbamazepine, have been reported to be associated with increased risks for major congenital malformations, while less is known about the teratogenic potential of the newer generation AEDs that have been introduced to the market during the last 20 years.

Epilepsy is a condition characterised by the occurrence of recurrent epileptic seizures, with potentially serious consequences. Uncontrolled seizures significantly affect the quality of life of the patient with epilepsy, and major convulsive seizures could be harmful and occasionally even fatal (Tomson et al. 2004a). In addition to these harmful effects on the person with epilepsy, maternal seizures during pregnancy may also adversely affect the foetus (Tomson and Hiilesmaa 2007). Hence, the potential adverse outcomes in the offspring due to maternal use of AEDs need to be weighed and balanced against the risks associated with the underlying disease itself. In epilepsy, the maternal and foetal risks with uncontrolled major convulsive seizures are generally considered to outweigh the teratogenic risks with AEDs. Treatment is therefore maintained also during pregnancy in women with active

epilepsy aiming at complete control of generalized tonic-clonic seizures (Tomson and Hiilesmaa 2007).

Women with epilepsy have been estimated to account for 0.3% up to 0.7% of all pregnancies (Gaily 1991; Viinikainen et al. 2006). The proportion of pregnancies with exposure to AEDs is probably even higher considering the increasing use of AEDs for other indications than epilepsy (Spina and Perugi 2004). The vast majority of these women will have uneventful pregnancies and give birth to perfectly normal children. However, the medical management during pregnancy is a matter of special concern since maternal epilepsy and AED treatment are associated with an increased risk for an abnormal pregnancy outcome.

2 Teratogenic Effects of AEDs: Methodological Issues

Many different methods have been used to assess the foetal risks associated with exposure to AEDs. The first years after the initial report on possible teratogenic effects of AEDs saw many publications of case-series of adverse pregnancy outcomes collected in individual centres or regions. A slightly more systematic method is spontaneous reporting of pregnancy outcome to the manufacturers, to drug agencies or surveillance programmes. Such methods can be useful in providing signals. However, reporting is selective, and since information on the denominator (total number of pregnancies exposed to the drug) is missing, these methods cannot be used for a proper risk assessment.

Case–control designs are generally considered useful for assessment of uncommon outcomes, such as birth defects. Cases with malformations are compared to controls regarding exposure to AEDs in foetal life. The method has been used to study the association between some specific malformations and exposure to individual AEDs, e.g. neural tube defects and exposure to valproate and oral clefts and lamotrigine. Case–control studies have also been utilised to analyse exposure to different AEDs and congenital abnormalities in general (Kjaer et al. 2007). A drawback of case–control studies is the risk of recall bias. Mothers of children with malformations are more likely to report drug intake during pregnancy.

Other studies have utilised existing general registries. Information on exposure could be obtained from a national drug prescription database (Artama et al. 2005) or from other registries that systematically and prospectively obtain information on drug intake in early pregnancy. The Swedish and Norwegian Medical Birth Registries are examples of the latter. These can be crosslink with registries of birth defects to assess the association between use of AEDs in early pregnancy and adverse outcome (Veiby et al. 2009; Wide et al. 2004). Such registries can have the advantage of recording exposure before pregnancy outcome is known and in addition being population-based, nationwide and thus representative. Contrarily, they often lack details on important information such as drug dosage, indication for treatment and classification of epilepsy, seizure control during pregnancy and on other factors that could contribute to the outcome. Furthermore, the teratogenic

outcome might not be classified according to uniform criteria and the assessor of the child might be influenced by information on drug intake during pregnancy.

Another common approach is cohort studies of pregnancies in women with epilepsy. Retrospective cohort studies (where women are included at a time when pregnancy outcome might be known) are associated with a risk of selection bias. This is avoided in prospective studies where women ideally are identified and enrolled in early pregnancy before any information on pregnancy outcome is known. Such studies have traditionally often been hospital based and many studies based on cohorts from single hospitals or epilepsy centres or from several collaborating clinics were published in the 1980s and 1990s (Tomson et al. 2004b). Additional advantages with such prospective cohort studies is that they usually have a reliable classification and details on the mothers' epilepsy, the course of the epilepsy during pregnancy and on other potential risk factors. The major disadvantage is that they represent selected epilepsy populations, probably more severe cases under specialist care. A further major limitation has been in the number of included pregnancies, often a few hundred and at best a thousand pregnancies (Tomson and Battino 2005).

Special types of cohort studies, antiepileptic drugs and pregnancy registries, were established in the late 1990s and have thus now been operational for more than a decade (Tomson et al. 2010). These registries are prospective observational studies enrolling women with epilepsy early in pregnancy collecting information on drug exposure and other potential risk factors before outcome of the pregnancy is known. Women are followed throughout pregnancy and the outcome in terms of occurrence of birth defects in the offspring is recorded. The advantage of such studies is that they may collect high numbers of pregnancies, the type of drug exposure is recorded in an unbiased way without prior knowledge of teratogenic outcome, and detailed data on other relevant patient characteristics could be obtained. They share the limitations of many previous cohort studies in being based on selected patients, which hampers the possibilities to generalize from the results and although they share many methodological features, there are also significant differences between them (Tomson et al. 2010).

The aforementioned studies are designed primarily to evaluate the risk of major congenital malformations. Assessment of postnatal cognitive development poses further difficulties and challenges. An extended follow-up is necessary. By this, however, environmental factors such as psycho-social factors, including maternal education, cognitive status and epilepsy may all affect the child's performance. The assessor needs to be blinded and appropriate controls included.

Even results of prospective studies of teratogenic effects of AEDs may be difficult to interpret. For obvious reasons, women considering pregnancy have not been randomised to different types of treatment. The selection of a particular treatment depends on individual environmental and genetic factors that could be linked to the risk of adverse pregnancy outcome. An association between exposure to a certain AED and occurrence of adverse pregnancy outcome in an observational study is thus not evidence of a causal relationship. The impact of possible confounders, such as type of epilepsy, seizure frequency, family history of birth

defects and exposure to additional risk factors needs to be assessed, which requires large sample sizes. It is thus important to pay attention to methodological issues such as statistical power, reliability of collected data, and attempts to control for appropriate confounding factors in the analyses, rather than to just compare rates of adverse pregnancy outcome in published studies.

3 Growth Retardation

Reduced birth weight, body length and head circumference in the offspring of women treated with phenytoin was reported already in the 1970s (Hanson et al. 1976). Such reductions in body dimensions were confirmed in subsequent studies of larger cohorts (Battino et al. 1992, 1999; Dessens et al. 2001; Hiilesmaa et al. 1981; Wide et al. 2000). In general, more pronounced effects were found in infants exposed to polytherapy, whereas the association between reduced body dimensions and specific AEDs in monotherapy varies. Phenobarbital and primidone have been implicated, whereas others have reported carbamazepine to be most strongly associated with small head circumference. A population-based Swedish study spanning 25 years, found a clear trend towards normalization of the head circumference in parallel with a shift from polytherapy towards monotherapy despite an increasing use of carbamazepine (Wide et al. 2000). Other more recent studies also suggest that, with present treatment strategies, microcephaly may no longer be more common among infants of mothers treated for epilepsy during pregnancy (Choulika et al. 1999). A very recent populations-based nationwide Norwegian study found low birth weight, small for gestational age, and small head circumference to be significantly more common in infants of mothers with epilepsy compared to the general population (Veiby et al. 2009). However, small for gestational age was more common in the offspring of mothers with epilepsy whether the mothers were taking AEDs or not.

A committee of the American Academy of Neurology and the American Epilepsy Society recently reassessed the evidence related to the care of women with epilepsy during pregnancy (Harden et al. 2009). The committee concluded that neonates of women with epilepsy taking AEDs probably have an increased risk of small for gestational age about twice the expected rate.

4 Minor Anomalies and Dysmorphisms

Minor anomalies are structural variations without medical, surgical or cosmetic importance. Discrete minor anomalies are frequently found in normal infants, but combinations of several anomalies can form a pattern, a dysmorphic syndrome, which may indicate a more severe underlying dysfunction. The term “foetal anticonvulsant syndrome” has been used to describe an AED-associated embryopathy

variably characterised by microcephaly, growth retardation, hypertelorism, depressed nasal bridge, low set ears, micrognathia and distal digital hypoplasia, other anomalies, and sometimes developmental delay (Dean et al. 2002; Holmes et al. 2001; Moore et al. 2000). More distinctive phenotypes have also been claimed to be associated with specific AEDs, most notably phenytoin, carbamazepine and valproate. Valproate exposure has been claimed to cause a somewhat different dysmorphic syndrome characterised by thin arched eyebrows with medial deficiency, broad nasal bridge, short anteverted nose, and a smooth long filtrum with thin upper lip. Such features have been suggested to be associated with, and indicative of, impaired cognitive development (Dean et al. 2002; Kini et al. 2006). The overlap in the various dysmorphisms is considerable and their drug specificity has therefore been questioned as has their predictive significance vs. cognitive development (Perucca and Tomson 2006). In addition, the pathogenesis is still somewhat controversial. Gaily et al. (1988) attributed most of the minor anomalies to genetic factors rather than drug exposure, although most studies suggest that there is an association between minor anomalies and exposure to AEDs. Indeed one study of infants of untreated mother with epilepsy failed to find any features of the foetal antiepileptic drug syndrome in the offspring (Holmes et al. 2000). It should, however, be underlined that minor anomalies are much more difficult to assess objectively than major malformations, and that the incidence of minor anomalies in exposed infants varies markedly between studies.

5 Major Congenital Malformations

5.1 Overall Malformation Rates with AEDs

Major congenital malformations are commonly defined as a structural abnormality with surgical, medical or cosmetic importance. Numerous studies from the 1980s and 1990s have confirmed increased rates of birth defects in children of mothers with epilepsy. The prevalence of major congenital malformations in children exposed to AEDs has ranged from 4 to 10%, corresponding to a two- to fourfold increase from the expected in the general population (Harden et al. 2009; Meador et al. 2008; Tomson and Battino 2005, 2009; Tomson and Hiilesmaa 2007). A few more recent studies, however, have not demonstrated increased risks in infants exposed to AEDs in utero compared to offspring of women with epilepsy not taking AEDs (Morrow et al. 2006; Veiby et al. 2009). In a prospective observational study from the UK, the relative risk of major congenital malformations among children of mothers with epilepsy taking AEDs during pregnancy vs. women with untreated epilepsy was 1.19 (0.59–2.40) (Morrow et al. 2006). In a nationwide population-based Norwegian registry study, the frequency of major malformations was 3.3% in children of mothers with treated epilepsy, not significantly different from the 2.5% among controls in the general population (Veiby et al. 2009).

Much of the variation in reported outcomes could be explained by differences in study methodology including study populations, in selection of control populations and in criteria for malformations. A possible decrease in recent years in the prevalence of malformations in offspring of women with epilepsy might also be related to changes in treatment strategies. It is possible that more frequent use of AED monotherapy as opposed to polytherapy, use of lower doses, changes in AED preferences, and pre-conceptional counselling has contributed to a more optimal management with reduced foetal risks. Nevertheless, it is still debated whether the usually reported increase in malformation rates is entirely caused by AEDs or if to some extent this could be linked to the underlying epilepsy disorder, or to seizures. The available data, however, strongly suggest that AED exposure is the major factor. In 26 cohort studies that included pregnancies of women with treated as well as untreated epilepsy, the average malformation rate among children exposed to AEDs in utero was 6.1% compared to 2.8% among children of mothers with untreated epilepsy and 2.2% in infants of healthy controls (Tomson and Battino 2009). These observations have been confirmed in a meta-analysis of the evidence of epilepsy per se as a teratogenic risk (Fried et al. 2004). Ten studies reporting rates of congenital malformations in offspring of untreated women with epilepsy were included. The malformation rate in this group was not higher than among offspring of non-epileptic healthy controls, odds ratio (OR) 1.92 (0.92–4.00). The OR was 0.99 (0.49–2.01) after removal of some small studies likely to be affected by publication bias.

Although obviously, untreated women with epilepsy are different in many respects from those who are under treatment during pregnancy, the available evidence strongly suggests that treatment is the major cause of increased risk of adverse pregnancy outcomes. Further support for a drug effect comes from the observation of greater risks with polytherapy compared to monotherapy with AEDs. Polytherapy was associated with a malformation rate of 6.8 vs. 4.0% in monotherapy in a recent pooled analysis (Tomson and Battino 2009).

5.2 Specific Malformations

The pattern of malformations associated with AEDs as a group is mostly similar to that seen in the general population. Cardiac defects are the most common followed by facial clefts, and hypospadia (Battino and Tomson 2007). There may, however, be an association between certain individual AEDs and some specific malformations. Neural tube defects and hypospadia are more common among offspring of mothers who used valproate during pregnancy (Morrow et al. 2006; Samrén et al. 1999), the risk of neural tube defects in association with valproate has been estimated to 1–2% (Lindhout and Schmidt 1986). An increased risk of neural tube defects of 0.5–1% has also been reported after carbamazepine exposure (Kallen 1994; Rosa 1991). Valproate has also been associated with facial clefts (Morrow et al. 2006) and phenytoin and carbamazepine with cleft palate

(Puho et al. 2007). Recent data from the North American AED Pregnancy Registry suggested a tenfold increase in risk of oral clefts among lamotrigine exposed infants (Holmes et al. 2008a), but this specific association has not been confirmed in other registries (Dolk et al. 2008; Holmes et al. 2008a). Exposure to phenobarbital has been suggested to increase the risk of cardiac malformations (Canger et al. 1999).

5.3 Comparative Malformation Rates with Different AEDs

For reasons discussed above, women with active epilepsy will need continued treatment throughout pregnancy. The relative safety during pregnancy is therefore a major criterion for selection of an AED for a woman with epilepsy who is of childbearing potential. Large studies are needed to draw conclusions on the relative teratogenic potential of different AEDs as the prevalence of birth defects with AEDs fortunately is no more than 4–10%. However, surprisingly few studies in the past have comprised more than 500 pregnancies in total. Clearly much larger cohorts are needed to permit a meaningful assessment of individual AEDs. During the last decade, some different strategies have been applied to achieve this.

One method, which has been used in the Nordic countries, is to utilise different existing national registries and databases for the purpose of assessing the safety of AED use in pregnancy. One example is the Swedish Medical Birth Registry, a nationwide population-based health registry compiled from antenatal maternal health clinic records, and those of the delivery and maternity wards. Drug exposure is recorded at the first visit to the maternity health clinics (typically gestational week 9). Pregnancy outcome is assessed based on registries of birth defects. A report from this registry was based on 1,398 pregnancies with exposure to AEDs (Wide et al. 2004). The odds ratio (OR) for having a malformation in the AED-exposed offspring, compared with the expected estimate from all infants born, was 1.86 (1.42–2.44) overall. OR in monotherapy exposed was 1.61 (1.18–2.19), and in polytherapy 4.20 (2.42–7.49). The OR was higher after exposure to valproate monotherapy compared with carbamazepine monotherapy 2.59 (1.43–4.68).

Another nationwide population-based study utilized the Finnish drug prescription database and the National Medical Birth Registry to identify all women who were prescribed AEDs during pregnancy (Artama et al. 2005), including 1,411 pregnancies with AED exposure. Congenital malformations were more common among offspring of these women (4.6%) than among offspring of untreated patients with epilepsy (2.8%). Compared with untreated patients, the risk of malformations was higher in foetuses exposed to valproate monotherapy (malformation rate 10.7%; OR = 4.18; 2.31–7.57) or valproate as part of polytherapy (malformation rate 9.2%; OR = 3.54; 1.42–8.11). In contrast, the risk of malformations was not elevated in association with exposure to carbamazepine, oxcarbazepine, or phenytoin monotherapy.

A third example is a recent study from Norway. The nationwide compulsory Medical Birth Registry of Norway was surveyed from 1999 to 2005 (Veiby et al.

2009). A total of 961 pregnancies with AED exposure were identified. An increased risk for major congenital malformations compared to unexposed could be demonstrated only for valproate monotherapy (5.6 vs. 2.5% in the general population) and AED polytherapy (6.1%).

The advantage of these studies is that they are population based and the results are likely to be representative. However, they lack detail concerning other potential risk factors, e.g. the indication for treatment and type of epilepsy, seizure control during pregnancy, AED dosage and other. Pregnancies ending in elective abortions are also not included even if the indication was foetal abnormalities. Most importantly, although nationwide, the number of included pregnancies on different specific AEDs is too small to permit a more precise comparison of their teratogenic potential.

In order to facilitate enrolment of greater numbers of pregnancies with AED exposure, and thus more meaningful comparisons, different groups established specific Epilepsy and Pregnancy Registries in the late 1990s (Tomson et al. 2010). Some were set up by pharmaceutical companies and collect data on the manufacturers' own product (e.g. GlaxoSmithKline's International Lamotrigine Registry) (Cunnington et al. 2007). Others have been established by independent research groups and include information on all AED exposures. These are national, regional (e.g. Australia, UK, North America, Kerala, India) or broadly international (European and International Registry of Antiepileptic Drugs in Pregnancy, EURAP). Many of the registries have now been operational for more than 10 years and are beginning to release results.

Malformation rates reported from pregnancy registries and from some other larger and contemporary studies are presented for the five most frequently used AEDs (valproate, carbamazepine, lamotrigine, phenobarbital and phenytoin) in Table 1.

In the absence of a comparator, the results from the company-sponsored registries are difficult to interpret. However, GlaxoSmithKline's International Lamotrigine Pregnancy Registry reported a malformation rate of 2.9% based on 802 monotherapy exposures (Cunnington et al. 2007).

The largest independent AED and pregnancy registries are The North American Antiepileptic Drugs and Pregnancy Registry (NAAPR), the United Kingdom Epilepsy and Pregnancy Register, and EURAP, an international registry enrolling pregnancies from more than 40 countries, in Europe, Australia, Asia, Oceania and South America (Tomson et al. 2010). These registries have enrolled 6,000–14,000 pregnancies and two of them, NAAPR and the UK register, have published results on teratogenic outcome. These three registries are slightly different in their scope and differ significantly in their methodologies, which should be kept in mind when malformation rates are compared across the registries.

NAAPR has reported increased malformation rates in comparison with the general population with phenobarbital monotherapy (6.5%), relative risk (RR) 4.2 (1.5–9.4) (Holmes et al. 2004), and valproate (10.7%) RR 7.3 (4.4–12.2) (Wyszynski et al. 2005). The malformation rate was 2.8% with lamotrigine monotherapy (Holmes et al. 2008a), 2.5% ($n = 873$) with carbamazepine and

Table 1 Rates of malformations,% and (number of monotherapy exposures) with antiepileptic drugs in monotherapy in some major studies

Study/registry	Valproate	Carbamazepine	Lamotrigine	Phenobarbital	Phenytoin
Samrén et al. (1997)	8.7% (184)	7.9% (280)		10.4% (48)	6.4% (141)
Samrén et al. (1999)	5.7% (158)	3.7% (376)		2.9% (172)	0.7% (151)
Kaneko et al. (1999)	11.1% (81)	5.7% (158)		5.1% (79)	9.1% (132)
GlaxoSmithKline (Cunnington et al. 2007)			2.9% (802)		
Finnish Drug prescription (Artama et al. 2005)	10.6% (263)	2.7% (805)			
Swedish Medical Birth Registry (http://www.janusinfo.org/)	7.7% (507)	5.4% (1,199)	4.9% (400)		7.6% (145)
UK Register (Morrow 2007, data on file of the UK Epilepsy Pregnancy Registry, personal communication)	6.2% (715)	2.2% (900)	3.2% (647)		3.7% (82)
North American Registry (Hernandez-Diaz et al. 2007; Holmes et al. 2004, 2008a, b; Wyszynski et al. 2005)	10.7% (149)	2.5% (873)	2.8% (684)	6.5% (77)	2.6% (390)
Australian Register (Vajda et al. 2007)	13.3% (166)	3.0% (234)	1.4% (146)		3.2% (31)
Norwegian Birth Registry (Veiby et al. 2009)	5.9% (204)	2.6% (454)	2.7% (260)	0% (14)	0% (19)

2.6% ($n = 390$) with phenytoin monotherapy (Hernandez-Diaz et al. 2007), not significantly increased from the background rate of 1.6%.

The UK register published their first report based on 3,607 cases (Morrow et al. 2006). The rate of major congenital malformations for pregnancies exposed to valproate monotherapy was 6.2% (4.6–8.2%) compared with 2.2% (1.4–3.4%) for carbamazepine. The malformation rate with lamotrigine monotherapy was 3.2% (2.1–4.9%) based on 647 pregnancies. Interestingly, the malformation rate in offspring of 227 untreated women with epilepsy was 3.5% (1.8–6.8%), very similar to the 3.7% (3.0–4.5%) among the monotherapy exposures in general ($n = 2{,}468$).

It is evident from Table 1 that malformation rates across studies vary considerably for the same AED in monotherapy. Carbamazepine exposure was associated

with rates ranging from 2.2 to 7.9%, lamotrigine from 1.4 to 4.9%, phenytoin from 0.7 to 9.1%, and valproate from 5.7 to 13.3% (Table 1). The wide ranges in malformation rates reflect differences in study populations, criteria and methodology. Prevalences of malformations with different AEDs should therefore not be compared across studies. However, there appears to be a consistent pattern within studies with higher rates with valproate and lower rates with carbamazepine and lamotrigine (Table 1). Even within-study comparisons should be made with caution considering the possible effects of confounding factors.

There is very limited published data on pregnancy outcome with other new generation AEDs than lamotrigine. Malformation rates in reports based on prospective pregnancies with monotherapy exposure to newer generation AEDs other than lamotrigine, such as gabapentin, topiramate, levetiracetam, oxcarbazepine and zonisamide, are shown in Table 2. Even when pregnancies from all available studies are added up, the total number of monotherapy exposures for each of gabapentin, topiramate, levetiracetam, oxcarbazepine is limited to approximately 250–300 pregnancies, and much less for zonisamide. Clearly these numbers are too small for a reliable assessment of the risks.

In their recent evidence-based review, the American Academy of Neurology and the American Epilepsy Society Committee concluded that it is highly probable that valproate exposure during the first trimester is associated with higher risk of major congenital malformations compared to taking carbamazepine, and possibly

Table 2 Monotherapy exposures to some newer generation antiepileptic drugs in different published studies, number of exposures (number of pregnancies with major malformations)

References	GBP	TPM	LEV	OXC	ZNS
Kondo et al. (1996)					4 (0)
Samrén et al. (1999)				2 (0)	
Fonager et al. (2000)	1 (0)			14 (0)	
Hvas et al. (2000)				7 (0)	
Long (2003)			3 (0)		
Montouris (2003)	16 (1)				
Kaaja et al. (2003)				9 (1)	
Meischenguiser et al. (2004)				35 (0)	
Swedish Medical Birth Registry (http://www.janusinfo.org/)	68(5)			4 (0)	
Artama et al. (2005)				99 (1)	
UK Registry 2007 (Hunt et al. 2006; Hunt et al. 2008; Morrow 2007, data on file of the UK Epilepsy Pregnancy Registry, personal communication)	31(1)	42(1)	39(0)		
Ornoy et al. (2008)		29(1)			
Ten Berg et al. (2005)			11 (0)		
Holmes et al. (2008a, b)	127(1)	197(8)	197(4)	121(2)	
Veiby (2010, personal communication)	7(0)	16(1)	15(1)	30(1)	
TOTAL	250 (8)	284(11)	265 (5)	321(5)	4 (0)

compared to phenytoin or lamotrigine (Harden et al. 2009). Other newer generation AEDs are not mentioned in this report.

6 Postnatal Cognitive Development

During the past 3 decades, several studies with different designs have aimed at assessing whether exposure to AEDs in utero could also adversely affect the cognitive development of the child after birth. Such studies are complicated to perform, requiring long-term follow-up. But they are also difficult to interpret because of confounding (e.g. parental cognitive function, socio-economic circumstances, maternal epilepsy) and in particular since environmental factors become more important with increasing age of the child. Few studies have been published, and mostly based on small cohorts. Studies from the 1980s and 1990s have aimed at assessing phenobarbital and more often phenytoin and carbamazepine, the most frequently used AEDs at that time. A prospective population-based study from Helsinki, Finland found no influence of AED (mainly phenytoin and carbamazepine) exposure on global IQ (Gaily et al. 1990). Observed cognitive dysfunction was attributed to maternal seizures and educational level of the parents rather than to the treatment. A Swedish population-based prospective study found no difference in psychomotor development in children exposed to carbamazepine compared with control children of healthy mothers, but a trend for phenytoin exposed children to do slightly worse in some tests of motor coordination (Wide et al. 2002). Scolnik et al. (1994) reported lower global IQ in children exposed to phenytoin but not in those exposed to carbamazepine.

A Cochrane Review from 2004 concluded that at that time there was little evidence about which drugs carry more risks than others to the development of children exposed (Adab et al. 2004b). Some subsequent studies, however, have suggested that exposure to valproate might carry a particular risk of adverse developmental effects (Adab et al. 2001; Meador et al. 2009; Vinten et al. 2005). A retrospective survey from the UK found additional educational needs to be more common among children that had been exposed to valproate than in those exposed to carbamazepine or unexposed control children (Adab et al. 2001). A more detailed investigation revealed lower verbal IQ in those exposed to valproate than in unexposed children and children exposed to carbamazepine or phenytoin (Adab et al. 2004a; Vinten et al. 2005). Multiple regression analysis identified exposure to valproate, frequent tonic-clonic seizures in pregnancy and low maternal IQ to be associated with lower verbal IQ also after adjustment for confounding factors.

Given the retrospective design, small numbers and poor participation rate, the results need to be interpreted with some caution. However, some subsequent prospective studies report similar observations concerning valproate. Hence, a small population-based prospective study from Finland found a lower verbal IQ in children exposed in utero to valproate monotherapy ($n = 13$) and to

polytherapy in general compared with non-exposed children or children exposed to carbamazepine (Gaily et al. 2004). However, the results were confounded by low maternal education and polytherapy. Another small prospective population-based Finnish study signals a similar trend for worse outcome in children exposed to valproate but also points to the problem of confounding factors as the mothers using valproate in pregnancy scored lower on IQ than other groups (Eriksson et al. 2005).

A larger, prospective observational study from Kerala, India, evaluated mental and motor development in children of mothers with epilepsy, but already at 15 months of age (Thomas et al. 2008). Children exposed to polytherapy had lower developmental quotients than those exposed to monotherapy. Compared with those exposed to carbamazepine monotherapy ($n = 101$), children exposed to valproate monotherapy ($n = 71$) had significantly lower mental and motor developmental quotients, whereas there was no significant difference between children exposed to other AEDs (mainly phenobarbital or phenytoin) compared with valproate. Of note is that this study did not analyse the possible influence of maternal cognitive function and outcome in the children.

The first reasonably powered truly prospective study of long-term cognitive effects of foetal exposure to AEDs recently published interim results (Meador et al. 2009). Between 1999 and 2004, women from USA and the UK on monotherapy with valproate, carbamazepine, lamotrigine or phenytoin were enrolled in early pregnancy in this observational study. The primary analysis in this study is a comparison of neurodevelopmental outcomes at 6 years of age, but interim results at 3 years of age have been released (Meador et al. 2009). In this carefully designed study, children exposed to valproate ($n = 53$) on average had an IQ score nine points lower than the score of those exposed to lamotrigine ($n = 84$), seven points lower than those exposed to phenytoin ($n = 48$) and six points lower than children exposed to carbamazepine ($n = 73$). IQ scores did not differ significantly among children exposed to the other three AEDs (lamotrigine, phenytoin, carbamazepine). These differences were obtained after adjustment for maternal IQ, infant's gestational age and some other potential confounding factors (Meador et al. 2009). It should, however, be noted that the IQ was within the normal range also among children exposed to valproate. There was also a significant correlation between the valproate dose in pregnancy and the child's IQ. In fact children exposed to valproate doses $<1{,}000$ mg/day did not differ in IQ from those exposed to other AEDs.

A few retrospective studies have suggested a specific association between exposure to valproate and the risk of developing autistic disorder (Rasalam et al. 2005), but this also needs further investigations.

The Committee of American Academy of Neurology and the American Epilepsy Society concluded that cognitive outcomes are probably reduced in children exposed to valproate compared to carbamazepine and possible also compared with phenytoin (Harden et al. 2009).

7 Dose-Dependency

A dose–effect relationship has so far been shown most consistently for teratogenicity in association with valproate. Dosages above 800–1,000 mg/day have thus been associated with significantly greater risks than lower dosages (Artama et al. 2005; Kaneko et al. 1999; Morrow et al. 2006; Samrén et al. 1997, 1999; Vajda et al. 2007). Data on cognitive outcome reveal a similar pattern. The retrospective study from Liverpool found that verbal IQ was no different from unexposed controls among children exposed to valproate doses <800 mg/day (Vinten et al. 2005). Likewise, the prospective NEAD study found IQ of children whose mothers took valproate in doses <1,000 mg/day to be similar to IQs in those exposed to other AEDs (Meador et al. 2009).

The UK Epilepsy and Pregnancy Register reported a positive dose response for major congenital malformations also for lamotrigine. Doses above 200 mg/day were associated with higher risks (Morrow et al. 2006). This pattern was, however, not found in the International Lamotrigine Registry of GlaxoSmithKline, nor did the North American pregnancy registry find lamotrigine doses to be significantly higher in mothers to children with malformations than in mothers to healthy children (Cunnington et al. 2007).

The American Academy of Neurology and the American Epilepsy Society Committee concluded that there is probably a relationship between the dose of valproate and lamotrigine and the risk of major congenital malformations (Harden et al. 2009).

8 Mechanisms of Teratogenesis

The mechanisms for the developmental toxicity of AEDs are likely to be multiple and also to partly vary with different AEDs. There is clearly an individual susceptibility as only a fraction of those exposed to the same treatment show signs of teratogenic effects. This is further supported by clinical observations of greater risks of AED-related embryopathy among siblings exposed to the same drug (Malm et al. 2002). A similar variability in the frequency and pattern of adverse pregnancy outcomes has been related to strain differences in experimental studies in mice (Buehler et al. 1990; Dean et al. 1999; Finnell 1991; Lindhout and Omtzigt 1992; Raymond et al. 1995; Strickler et al. 1985; Volcik et al. 2003). The outcome likely depends on gene–environment interactions and susceptible embryos probably carry genetic factors determining their susceptibility to AED-induced adverse foetal effects (Zhu et al. 2009).

A favoured hypothesis for many years suggests that the developmental toxicity of AEDs is related to their interference with folate metabolism. Folates are co-factors involved in the biosynthesis of nucleic acids and in the re-methylation of homocysteine to methionine. Many AEDs, including phenobarbital, phenytoin, primidone

and carbamazepine, are known to reduce folate levels. Some clinical studies have reported an association between low maternal serum folate levels and risk of malformations (Dansky et al. 1987; Ogawa et al. 1991), although this has not been a consistent finding. In humans, extra periconceptional supplementation with folate has been demonstrated to reduce the risk of neural tube defects and at higher doses also the risk of recurrence in high-risk groups (MRC 1991). It is, however, important to understand that women with epilepsy were excluded from these studies. Observational data from epilepsy and pregnancy registries have unfortunately not demonstrated any protective effect against adverse pregnancy outcomes of periconceptional folate supplementation to women with epilepsy (Morrow et al. 2009).

The 5,10 methylene tetrahydrofolate reductase (MTHFR) gene has been suggested as one candidate to explain genetic susceptibility to folate sensitive malformations (Dean et al. 1999). MTHFR is involved in the biotransformation of folate and is highly polymorphic. Some mutations have been associated with increased risks of malformations such as neural tube defects, cleft palate and congenital heart disease that are often seen in relation to exposure to AEDs.

Bioactivation of AEDs to toxic reactive intermediate metabolites has been another suggested mechanism for the teratogenic effects (Amore et al. 1997; Bennett et al. 1996; Buehler et al. 1994; Finnell et al. 1995; Finnell and Dansky 1991; Lillibridge et al. 1996; Lindhout et al. 1984; Martz et al. 1977; Pantarotto et al. 1982; Rane and Peng 1985; Roy and Snodgrass 1990; Strickler et al. 1985). Reactive epoxides could be the result of CYP450 mediated oxidation of phenytoin, carbamazepine or phenobarbital. Individual differences in rates of their formation and in their elimination could contribute to the individual susceptibility to adverse outcomes. This could be genetically determined as well as affected by interactions between different AEDs. However, some of the most potent teratogenic AEDs such as trimethadione lack the premises to form epoxides. Additionally, the CYP450 activity in the embryo during the sensitive periods is very low.

Another postulated bio-activating pathway is co-oxidation of AEDs to free radical intermediates. These could release reactive oxygen species (ROS), which may cause oxidative stress and thus teratogenicity. Deficiency of free radical scavenging enzymes, responsible for eliminating ROS, has been associated with malformations in the offspring of epileptic mothers exposed to AEDs (Parman et al. 1998; Wells et al. 1997; Wells and Winn 1996).

A more recent hypothesis suggests that many AEDs, such as phenytoin, trimethadione, carbamazepine, phenobarbital, and possibly lamotrigine may exert their teratogenic effects by inducing embryonic cardiac arrhythmia during specific sensitive restricted periods (Danielsson et al. 2000). These effects on the embryonic heart have been linked to the drugs' ability to block the rapid component of the delayed rectifying K ion current, Ikr (Azarbayjani and Danielsson 2002). It is postulated that the embryonic arrhythmia will cause temporary hypoxia followed by re-oxygenation and generation of ROS, which will cause tissue damage. Orofacial clefts, heart defects, distal digital defects and growth retardation could be hypoxia related and thus explained by such mechanisms.

A different proposed mechanism postulates that the teratogenic effects of AEDs may be explained by induction of neural apoptosis. Animal experiments have demonstrated apoptotic neurodegeneration in the developing brain induced by therapeutic concentrations of AEDs such as valproate, phenytoin, and phenobarbital (Bittigau et al. 2002; Kluger and Meador 2008).

It is clear that the mechanisms behind developmental toxicity of AEDs are presently far from completely understood. They are likely to be multiple and differ between individual AEDs and it is even conceivable that each individual AED can exert its adverse effects through more than one mechanism.

9 Conclusions

It has been known for more than 40 years that children of mothers with epilepsy have an increased risk of adverse pregnancy outcomes. Although multifactorial, the greater risk is mainly due to teratogenic effects of the AEDs. However, due to the significant maternal and foetal risks associated with uncontrolled epileptic seizures, AED treatment is generally maintained during pregnancy in the majority of women with active epilepsy.

Adverse pregnancy outcomes that have been associated with AED exposure include foetal growth retardation, major congenital malformations and impaired postnatal cognitive development. In earlier publications, the prevalence of major malformations in children exposed to AEDs has been 2–4 times higher than in the general population. More recent studies suggest a smaller increase in malformation rates. This seemingly more favourable outcome may be relating new treatment strategies with less polytherapy, lower AED dosages and different AED selection. Recent data from large prospective pregnancy registries have revealed differences between AEDs in their teratogenic potential. Malformation rates have consistently been higher in association with exposure to valproate than with carbamazepine and lamotrigine. Other, albeit more limited, prospective cohort studies also indicate reduced cognitive outcome in children exposed to valproate compared to carbamazepine and possibly lamotrigine. Information on pregnancy outcomes with newer generation AEDs other than lamotrigine are still insufficient.

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