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Review

Major congenital malformations in children of women with epilepsy

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ABSTRACT

It has been long known that the risk of major congenital malformations is increased among children of mothers with epilepsy. This is mainly due to the teratogenic effects of antiepileptic drugs although other factors, such as genetically determined individual susceptibility, are likely to contribute. Recent large scale prospective epilepsy and pregnancy registries have indicated that the rate of major congenital malformations may be at most two-fold higher than expected with exposure in utero to the presently most frequently used antiepileptic drugs such as carbamazepine or lamotrigine. Higher rates are consistently reported with exposure to valproate. The risk of teratogenic effects appears to be dose dependent and the lowest effective dose should thus be established before pregnancy regardless of which antiepileptic drug the woman is taking. Major changes such as switches between drugs should be avoided when pregnancy is established.

1. Introduction and background

In 1968 Meadow reported oro-facial clefts and other abnormalities among babies of mothers who received primidone, phenytoin, or phenobarbital [1]. Over the more than 50 years since this first report of birth defects in children exposed in utero to antiepileptic drugs (AEDs), subsequent studies have confirmed higher birth defects rates among children of mothers with epilepsy [2,3]. Research since the initial report have also demonstrated a broader picture of developmental toxicity of AEDs, which in addition to major congenital malformations (MCM) includes potential adverse effects on intrauterine growth [4], on cognitive development of the exposed child [5], and on the behavioral development [6]. The reasons for the increased risks are multifactorial and may include genetic factors, the maternal epilepsy and seizures during pregnancy, socio-economic status, but accumulating data strongly suggest that AEDs are the main reason for the increased risks [7]. A pooled analysis of data from 26 studies reported an MCM rate of 6.1% in offspring that had been exposed to AEDs compared to 2.8% in children of untreated women with epilepsy, and 2.2% in offspring of mothers without epilepsy [8]. Similar results were reported in a formal meta-analysis of 10 studies. The offspring of women with epilepsy who received AEDs had higher prevalence of MCM than controls (odds ratio (OR) 3.26; 95% CI 2.15–4.93), while the risk for MCM in the offspring of women with untreated epilepsy was not significantly higher than among non-epilepsy controls (OR 1.92; 95% CI 0.92–4.00) [9].

The present review will focus on the risk of MCM in offspring of women with epilepsy and in particular the role of AEDs and possible differences between drugs in their potential to cause MCM. The topic has been covered in previous reviews and guidelines [2,7], so emphasis in the present article will be on the more recent publications.

2. Methodological considerations

Studies aiming at assessment of the risk of MCMs in children exposed to AEDs in utero face many challenges in particular when the objective is to compare risks associated with different AEDs. For obvious ethical reasons randomized studies are not possible. We are restricted to observational studies with the potential problems of confounding by other risk factors than the AEDs, e.g. impact of seizures, type of epilepsy and related or unrelated genetic factors, and socio-economic circumstances. Second, fortunately the vast majority of pregnancies in the general population as well as in women with epilepsy result in healthy offspring without MCMs. As a consequence large numbers are needed for meaningful analyses where adjustments can be made for potential confounding factors. Even larger studies are necessary

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for assessment of individual specific MCMs. Avoiding selection or reporting bias is another challenge. It is more likely that adverse pregnancy outcomes are reported compared with normal outcomes. It is therefore essential that information on exposure, i.e. the AED treatment, is obtained, and enrollment achieved, before outcome of the pregnancy is known. This is best accomplished in prospective registries where pregnancies are enrolled in early pregnancy before any information on outcome is available. This is becoming more and more difficult as prenatal diagnostic tests are used earlier in pregnancy. Yet another challenge is the question of a comparison or control group. Some studies are restricted to internal comparisons between different AEDs, whereas others compare MCM rates among AED exposed with pregnancy outcomes in the general population, or in offspring of untreated women with epilepsy. The identification of MCMs depends on the vigilance of the observer as well as the time window of observation. It is therefore essential that exposed cases and unexposed controls are followed in an identical way.

Traditionally, the first suspicion of associations between drug use in pregnancy and occurrence of MCM has come from spontaneous reporting to manufacturers or regulators, or from retrospective case reports. These provide signals that need to be confirmed or refuted in epidemiological studies, with case–control or a cohort design. In case–control studies, cases with a birth defect are compared with controls, children without the defect, with regard to exposure to AEDs. Such studies are particularly useful when the event of interest is rare, such as a specific uncommon birth defect. A problem with many case–control studies is that the information on AED use is obtained after the pregnancy outcome is known, with an inherent risk of recall bias, and an over-estimation of risks. In addition, while providing a measure of the association between exposure to a specific AED and birth defects, case–control studies do not provide information on the frequency of the malformations in children exposed to the particular treatment or to comparators.

Cohort studies can be used to evaluate outcome of pregnancies with a certain drug. Ideally, information on exposure is obtained and enrollment in prospective cohort studies completed before outcome is known, thus avoiding recall bias. Some countries, e.g. in Scandinavia, have National Medical Birth Registers where information on maternal drug intake is recorded in early pregnancy and outcome of pregnancy obtained through other linked national registers. Such Medical Birth Registers have been used to assess risks for MCM in association with maternal use of AEDs [4,10]. They have the advantage of being population-based, and thus representative, and also to provide the outcome in the general population as control. There are also limitations: they lack information on the type of epilepsy (the Swedish Medical Birth Registry in fact does not specify the indication for the treatment), occurrence of seizures during pregnancy, details about drug dose, and many other potentially relevant risk factors. Pregnancies ending in induced abortions (due to detected MCM or for other reasons) are excluded in some [10], which underestimates the risk.

Epilepsy/antiepileptic drug and pregnancy registers were established in different countries some 15 years ago. These prospective observational studies have the specific objective to assess and compare risks for MCM with maternal use of different AEDs during pregnancy [11] and have by now each collected thousands of pregnancies with AED use. These registers are not population-based, but they contain much more detailed information on AED exposure, types of epilepsy, seizure frequency during pregnancy, and several other risk factors that are not available in the Scandinavian Medical Birth Registers. Although the basic principles of the epilepsy and pregnancy registers are similar, they differ slightly in some regards, e.g. methods for enrollment, exclusions, outcome criteria and time window for assessment of outcome. Their results are thus not immediately comparable [11].

The North American AED Pregnancy Registry (NAAPR) enrolls pregnant women from the US and Canada. The UK and Ireland Epilepsy and Pregnancy Register includes pregnancies from the UK and Ireland. EURAP is an international registry enrolling pregnant women from more than 40 countries world-wide. The Australian Pregnancy Register and the Kerala Registry of Epilepsy and Pregnancy in India are part of the EURAP collaboration but also publish independently [11]. These observational studies have provided much information in recent years that has had a direct impact on clinical practice, and the results will be summarized in the present review.

A different type of antiepileptic drugs and pregnancy registers are those organized by a pharmaceutical company, where the GlaxoSmithKline International Lamotrigine Register is the most established example [12]. A major drawback of these registers is that they only include pregnancies with the companies' own product, one specific antiepileptic drug, without comparators. This makes it difficult to draw meaningful conclusions since MCM rates, for reasons discussed above, cannot be compared across registers.

3. Different types of MCMs

Malformations among offspring of women with epilepsy are not unique but generally follow a pattern similar to what is seen in the general population with cardiac defects being the most common followed by facial clefts, and hypospadias, but with some variation between different AEDs. A pooled analysis of data from 21 prospective studies looked at four different groups of MCMs (cardiac, neural tube defects, oro-facial clefts, and hypospadias) associated with monotherapy exposure to the five most commonly used AEDs in these studies [2]. Cardiac malformations were the most frequent of the four MCMs for carbamazepine, lamotrigine, barbiturates, and phenytoin, whereas neural tube defects were the most common for valproate. Cardiac malformations appeared more frequently with barbiturates than with any of the other AEDs, whereas neural tube defects and hypospadias were more prevalent with valproate than with the other AEDs.

NAAPR reported a prevalence of oral clefts of 7.3/1000 infants exposed to lamotrigine monotherapy, a 10-fold increased rate compared to unexposed infants [13]. The prevalence of oral clefts among lamotrigine exposed was lower, 2.5/1000, in five other registries [13.] A population-based European case–control study found no evidence for a specific increased risk of orofacial clefts versus other malformations due to lamotrigine, but the study was not designed to assess whether there is a general increased risk of malformations with lamotrigine [14]. NAAPR has also observed a 10-fold increase in the rate of oro-facial clefts among infants exposed to topiramate monotherapy compared to unexposed [15]. A multi-database cohort study recently reported a prevalence of non-syndromic oral clefts 5.4 times higher among children exposed to topiramate in utero compared to unexposed children [16].

Case–control studies based on EUROCAT data have investigated the risks for specific MCMs with valproate exposure compared with no use of an AED. Valproate was associated with increased risks for spina bifida OR 12.7 (95% CI 7.7–20.7), atrial septal defect 2.5 (95% CI 1.4–4.4), cleft palate 5.2 (95% CI 2.8–9.9), hypospadias 4.8 (95% CI 2.9–8.1), polydactyly 2.2 (95% CI 1.0–4.5), and craniosynostosis 6.8 (95% CI 1.8–18.8) [17]. In a similar case–control study the only specific malformation associated with exposure to carbamazepine monotherapy was spina bifida, OR 2.6 (95% CI 1.2–5.3) compared with no AED [18]. Although these data can inform about associations between a particular AED and specific malformations, they rarely provide the direct comparison

of risks between different drugs. Such comparative data are generally derived from the pregnancy registries. Reported rates of the more common MCMs in the different major registries are summarized by AED in Tables 1a–1e.

4. Overall rates of major congenital malformations

Rates of MCMs with different monotherapy exposures from the four major epilepsy and pregnancy registries are summarized in Table 2. Included are also data from the Norwegian and Swedish Medical Birth Registers and from GSKs International Lamotrigine Registry [19–24]. As obvious from Table 2, MCM rates associated with any specific AED vary across the different registers, which can be explained by the methodological differences discussed above. However, some consistent patterns are seen within each register. First, with few exceptions the MCM prevalence is highest in association with valproate exposure in all registers, ranging from 4.7% to 13.8%. MCM rates with the two most frequently used AEDs, carbamazepine and lamotrigine, are lower than with valproate in all registers, and comparable between themselves in most studies. The MCM rate with phenobarbital is reported in three registers, and appears to be in between rates reported for lamotrigine/carbamazepine and valproate. MCM rates with phenytoin are highly variable, from 2.4% to 6.7% and based on few exposures in most registers. The prevalence of MCMs with levetiracetam appears to be low and so far in a similar range as lamotrigine/carbamazepine although the number of exposures are still much lower than for these older AEDs. Exposures to topiramate are too few to draw firm conclusions but the data from most registers indicate a higher prevalence than with lamotrigine/carbamazepine although in general not as high as with valproate. It should be emphasized that the precision of the estimates with newer AEDs such as levetiracetam, oxcarbazepine, and topiramate is still unsatisfactory due to the limited number of exposed pregnancies. This is even more the case with other newer generation AEDs such as gabapentin, pregabalin, zonisamide and lacosimide, which is why such data are not included here.

Polytherapy with AEDs has traditionally been considered a risk factor and associated with increased risk of MCM [3,7,8]. However, this is not a consistent pattern. Analysing data from the Australian register, and reviewing the literature, Vajda and colleagues concluded that the fetal hazard of AED polytherapy relative to

Table 1a
Prevalence, *n* (%), of more common specific major congenital malformations among infants exposed to lamotrigine monotherapy.

Source	Cardiovascular	Orofacial clefts	Hypospadia*	Neural tube defects	Others
EURAP [19]	8 (0.63)	2 (0.16)	4 (0.31)	0	
NAAPR [20]	3 (0.19)	7 (0.45)	0	2 (0.13)	
UK Ireland [21–23]	9 (0.4)	2 (0.1)	10 (0.5)	2 (0.1)	
GSK International [12]	11 (0.61)	2 (0.11)	2 (0.11)	3 (0.17)	

* NAAPR only included male offspring as denominator.

Table 1b
Prevalence, *n* (%), of more common specific major congenital malformations among infants exposed to carbamazepine monotherapy.

Source	Cardiovascular	Orofacial clefts	Hypospadia*	Neural tube defects	Others
EURAP [19]	22 (1.57)	2 (0.14)	9 (0.64)	5 (0.36)	
NAAPR [20]	3 (0.29)	5 (0.48)	1 (0.19)	3 (0.29)	
UK Ireland [21–23]	14 (0.8)	4 (0.2)	5 (0.3)	4 (0.2)	

* NAAPR only included male offspring as denominator.

Table 1c
Prevalence, *n* (%), of more common specific major congenital malformations among infants exposed to valproate monotherapy.

Source	Cardiovascular	Orofacial clefts	Hypospadia*	Neural tube defects	Others
EURAP [19]	22 (2.18)	4 (0.40)	17 (1.68)	11 (1.09)	
NAAPR [20]	8 (2.5)	4 (1.2)	5 (3.1)	4 (1.2)	
UK Ireland [21–23]	14 (1.1)	13 (1.1)	15 (1.2)	13 (1.1)	

* NAAPR only included male offspring as denominator.

Table 1d
Prevalence, *n* (%), of more common specific major congenital malformations among infants exposed to phenobarbital monotherapy.

Source	Cardiovascular	Orofacial clefts	Hypospadia*	Neural tube defects	Others
EURAP [19]	6 (2.76)	1 (0.46)	1 (0.46)	1 (0.46)	
NAAPR [20]	5 (2.5)	4 (2.0)	1 (0.97)	0	

* NAAPR only included male offspring as denominator.

Table 1e
Prevalence, *n* (%), of more common specific major congenital malformations among infants exposed to levetiracetam monotherapy.

Source	Cardiovascular	Orofacial clefts	Hypospadia	Neural tube defects	Others
NAAPR [20]	1 (0.22)	0	0	1 (0.22)	
UK Ireland [21–23]	0	0	0	0	

Table 2
Overall rates (%) of major congenital malformations (malformed/exposed) for different monotherapies. Data from different prospective registers.

Source	General population	Untreated epilepsy	Valproate	Carbamazepine	Lamotrigine	Phenobarbital	Phenytoin	Levetiracetam	Oxcarbazepine	Topiramate
EURAP [19]			9.7% (98/1010	5.6% (79/1402	2.9% (37/1280)	7.4% (16/217)	5.8% (6/103)	1.6% (2/126)	3.3% (6/184)	6.8% (5/73)
NAAPR [20]		1.1% (5/442)	9.3% (30/323)	3.0% (31/1033)	1.9% (31/1562)	5.5% (11/199)	2.9% (12/416)	2.4% (11/450)	2.2% (4/182)	4.2% (15/359)
UKIre [21–23]			6.7% (82/1220)	2.6% (43/1657)	2.3% (49/2098)		3.7% (3/82)	0.7% (2/304)		4.3% (3/70)
AUS [25]		3.3% (5/153	13.8% (35/253)	5.5% (19/346)	4.6% (14/307)		2.4% (1/41)	2.4% (2/84)	5.9% (1/17)	2.4% (1/42)
NMBR [4]	2.9%	2.8%	6.3% (21/333)	2.9% (20/685)	3.4% (28/833)	7.4% (2/27)		1.7% (2/118)	1.8% (1/57)	4.2% (2/48)
SMBR*	2.1%		4.7% (29/619)	2.7% (38/1430)	2.9% (32/1100)		6.7% (8/119)	(0/61)	3.7% (1/27)	7.7% (4/52)
GSK [12]					2.2% (35/1558)					

* As reported in Ref. [2].

monotherapy may depend more on the degree of exposure to valproate than the number of drugs [25]. This is supported by data from NAAPR, where the prevalence of MCM was 9.1% for lamotrigine combined with valproate, 2.9% for valproate plus any AED other than valproate, and 1.9% in association with lamotrigine monotherapy [26]. Likewise, the prevalence of MCM with carbamazepine plus valproate was 15.4%, compared with 2.5% for carbamazepine in combination with any other AED, and 2.9% for carbamazepine in monotherapy [26].

5. Dose-dependency

EURAP reported that in monotherapy the risk of MCM increases dose-dependently with all four assessed AEDs, carbamazepine, lamotrigine, valproate, and phenobarbital [19]. The dose-dependency remained when ten covariates were included in the multivariable analysis. The lowest malformation rates (2.0%; 1.19–3.24) were observed with less than 300 mg/day of lamotrigine at the time of conception and with carbamazepine of less than 400 mg/day (3.4%; 1.11–7.71). The lowest dose category analyzed for valproate, less than700 mg/day was associated with a malformation rate of 5.6%.

Dose-dependency of the MCM risk associated with valproate has been demonstrated in other registers, including the Australian, UK and Ireland, and NAPPR [20,21,27]. Malformation rates at different dosages of valproate, carbamazepine and lamotrigine in EURAP and UK and Ireland registers are summarized in Table 3. Suggested cut offs for greater risks have however varied somewhat but the registers defined dose exposure in different ways. While EURAP used dose at the time of conception [19], other registers have used the average dose during the first trimester. NAAPR reported a median average valproate daily dose during the first trimester of 1000 mg for pregnancies with MCM and 750 mg for those without [20]. The lowest MCM rates (<5%) with valproate were seen at doses up to 500 mg/day [20]. However, NAAPR did not find any apparent dose trend for other AEDs. The UK and Ireland register reported a significant dose effect with valproate and carbamazepine and a non-significant trend toward higher MCM rate with increasing dose of lamotrigine [21]. The mean daily dose of valproate was significantly higher for infants with MCMs (1031 mg) compared with those without (898 mg). The MCM rate with the lowest dose category for valproate (up to 600 mg/day) was 5.0% compared with 1.9% for carbamazepine at doses up to 500 mg/day, and 2.1% for lamotrigine up to 200 mg/day.

These data support the general strategy of aiming at the lowest effective dose of an AED for women planning pregnancy.

6. Other risk factors

It is obvious that there is an individual susceptibility to the teratogenic effects of AEDs as pregnancies with similar exposure in terms of type and dose of AEDs can result in MCMs as well as in normal outcomes. Genetic factors are likely to contribute. EURAP included 11 different non-drug related co-variates in a multivariable logistic analysis, and parental history of MCM came out as a significant risk factor with an OR of 4.4 (95%CI 2.1–9.2) [19]. Other registers have analyzed the recurrence risk of MCM in repeat pregnancies. The Australian register found that women on AEDs who had given birth to an infant with MCM in their first pregnancy, and who continued on the same AED, had a risk of 35.7% of having a child with MCM in their next pregnancy, compared with the expected rate of 3.1% [28]. The recurrence risk was even greater for women on valproate, 57.2%. The UK pregnancy register combined minor and major malformations in their analysis, and reported a 16.8% risk of having another child with such congenital malformations if the first child was affected, compared with 9.8% risk

Table 3
Rates of major congenital malformations (95% CI) with monotherapy with valproate, carbamazepine, and lamotrigine at different dose levels in EURAP and UK Ireland Registers.

Drug	EURAP [19]			UK Ireland [21]		
	Dose range mg/d	Number of exposed	MCM % (95% CI)	Dose range mg/d	Number of exposed	MCM % (95% CI)
Valproate	<700	431	5.6% (3.60–8.17)	<600	476	5.0%(3.4–7.4)
	≥700 < 1500	480	10.4% (7.83–13.50)	>600–<1000	426	6.1% (4.2–8.8)
	≥1500	99	24.2% (16.19–33.89)	>1000	297	10.4% (7.4–14.4)
Carbamazepine	<400	148	3.4% (1.11–7.71)	<500	721	1.9% (1.2–3.2)
	≥400 < 1000	1047	5.3% (4.07–6.89)	>500–<1000	739	2.7% (1.8–4.1)
	≥1000	207	8.7% (5.24–13.39)	>1000	170	5.3% (2.7–9.5)
Lamotrigine	<300	836	2.0% (1.19–3.24)	<200	1143	2.1% (1.4–3.1)
	≥300	444	4.5% (2.77–6.87)	>200–<400	665	2.4% (1.5–4.0)
				>400	267	3.4% (1.9–6.5)

for women whose first child did not have a malformation [29]. Unfortunately, these studies could not assess the recurrence risk if treatment was changed from first to second pregnancy, since most women remained on the same AED. Nevertheless, these observations lend further support to the importance of a genetic influence on the teratogenic risks associated with AEDs.

7. Conclusions

Our knowledge concerning the risks of MCM in association with exposure to AEDs has increased substantially thanks to the epilepsy and pregnancy registers. A major conclusion is that overall the increase in the risk with the frequently used AEDs carbamazepine and lamotrigine in monotherapy is not as great as previously thought. On the other hand valproate appears to be consistently associated with a greater risk than other AEDs in monotherapy as well as in part of polytherapy. The patterns of MCM also vary with the type of AED where a specific association between valproate and neural tube defects has been demonstrated.

The risk of teratogenic effects appears to be dose dependent, which has been most clearly demonstrated for valproate, where the risk seems to increase at doses above 500 mg/day although suggested cut-offs vary between registers. These observations highlight the importance of aiming for the lowest effective dose before conception.

Knowledge of the teratogenic potential of newer generation AEDs other than lamotrigine is limited. Data on levetiracetam are accumulating, and so far suggest MCM rates similar to those seen with lamotrigine or carbamazepine, whereas signals indicate higher rates with topiramate.

Conflict of interest statement

T.T. received research grants and/or speakers honoraria from Eisai, GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Sanofi-Aventis and UCB-Pharma. D.B. has received speakers fees from UCB Pharma. H.X. has nothing to declare.

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