Teratogenicity of antiepileptic drugs

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Purpose of review
We review data on the comparative teratogenicity of antiepileptic drugs (AEDs), focusing on major congenital malformations (MCMs), intrauterine growth restriction, impaired cognitive development, and behavioral adverse effects following prenatal exposure.

Recent findings
Prospective registries and meta-analyses have better defined the risk of MCMs in offspring exposed to individual AEDs at different dose levels. Valproate is the drug with the highest risk, whereas prevalence of MCMs is lowest with lamotrigine, levetiracetam, and oxcarbazepine. For valproate, phenobarbital, phenytoin, carbamazepine, and lamotrigine, the risk of MCMs is dose-dependent. Prenatal exposure to valproate has also been confirmed to cause an increased risk of cognitive impairments and autistic traits. In a population-based study, the risk of AED-induced autistic traits was attenuated by periconceptional folate supplementation.

Summary
The risk of adverse fetal effects differs in relation to the type of AED and for some AEDs also the daily dose. Although for MCMs the risk is primarily associated with the first trimester of gestation, influences on cognitive and behavioral development could extend throughout pregnancy. Available information now permits a more rational AED selection in women of childbearing potential, and evidence-based counseling on optimization of AED treatment before conception.

Keywords
antiepileptic drugs, behavior, cognition, congenital malformations, epilepsy, pregnancy

INTRODUCTION

Prospective studies have provided in recent years new information on the comparative teratogenic risks of antiepileptic drugs (AEDs), enabling a more rational approach to the management of epilepsy in women of childbearing potential. Largely, this information comes from registries initiated some 20 years ago, each enrolling thousands of pregnancies and assessing rates of major congenital malformations (MCMs) following exposure to different AEDs [1–4,5▪▪]. Smaller scale prospective cohort studies provided comparative data on neurodevelopment of children born from mothers taking AEDs during their pregnancy [6,7]. Recently, nationwide population-based healthcare registries from Scandinavia were utilized to assess risks for intrauterine growth restrictions and autism spectrum disorders in children exposed *in utero* to different AEDs [8–10] A consistent finding throughout these studies is the high risks associated with valproate [11], which prompted the European Medicines Agency to issue further restrictions on its use in girls and women of childbearing potential [12].

Although the sensitive period for induction of MCMs is limited to the first trimester, exposure throughout pregnancy is likely to impact on fetal growth and neurodevelopment. This review will discuss these three aspects of teratogenicity with emphasis on data from the last few years.

MAJOR CONGENITAL MALFORMATIONS

MCMs are defined as structural abnormalities of surgical, medical, functional, or cosmetic importance and can be classified according to different

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KEY POINTS

- The teratogenic risks vary substantially between AEDs.
- Exposure to valproate is associated with greatest risks for malformations as well as for cognitive and behavioral abnormalities.
- Teratogenic risks are dose-dependent for some AEDs.
- Exposure to lamotrigine, levetiracetam, and oxcarbazepine is associated with the lowest risk for malformations.
- Data on teratogenic risks with most newer generation AEDs is insufficient.

criteria [13]. Their severity and impact of quality of life can vary considerably. Therefore, it is important to assess not only the overall prevalence of MCMs with different AEDs but also the types of MCMs that they may induce. Pooling prospective data from 32 cohort studies revealed different patterns of MCMs with exposure to different AED monotherapies [11]. Barbiturates were associated with a high frequency of cardiac malformations, and valproate with increased risks of neural tube defects and hypospadias. In addition to confirming the association between barbiturates and cardiac malformations, a systematic Cochrane review found that exposure to valproate was associated with increased risks not only for neural tube defects but also for cardiac, orofacial/craniofacial clefts, and skeletal and limb malformations in comparison to other AEDs [14▪]. Another systematic review compared the prevalence of specific MCMs in offspring exposed to newer AEDs with that in the general population [15] and reported an association between topiramate and cleft lip with/without cleft palate and with hypospadia. The risk of cleft has been suggested to increase with the topiramate dose [16].

Regarding the overall risk of MCMs, a Cochrane meta-analysis of 31 observational studies reported that the highest prevalence was found in children exposed to valproate [10.93%, 95% confidence interval (CI), 8.91–13.13], for whom the risk ratio of MCMs was 5.69 (95% CI, 3.33–9.73) compared with children born to women without epilepsy and 3.13 (95% CI, 2.16–4.54) compared with those born to women with untreated epilepsy [14▪]. Increased risks were also noted for other AEDs. Compared with the offspring of women without epilepsy, the risk ratio was 3.69 (95% CI, 1.36–10.07) for topiramate, 2.84 (95% CI, 1.57–5.13) for phenobarbital, 2.38 (95% CI, 1.12–5.03) for phenytoin, and 2.01 (95% CI, 1.20–3.36) for carbamazepine. There was no increased risk for lamotrigine. Although no increased risk was identified after exposure to gabapentin, levetiracetam, oxcarbazepine, primidone, or zonisamide, interpretation of data for these AEDs was limited by small sample sizes [14▪]. A network meta-analysis based on 96 studies used as controls children unexposed to AEDs *in utero*, for whom the prevalence of MCMs was 2.6% [17]. Compared with controls, odds ratios (ORs) for MCMs were significantly increased for many AEDs used in monotherapy. The OR was highest for ethosuximide (3.04; 95% CI, 1.23–7.07), followed by valproate (2.93; 95% CI, 2.36–3.69), topiramate (1.90; 95% CI, 1.17–2.97), phenobarbital (1.83; 95% CI, 1.35–2.47), phenytoin (1.67; 95% CI, 1.30–2.17), and carbamazepine (1.37; 95% CI, 1.10–1.71). No increased risk was identified for lamotrigine (OR, 0.96; 95%, CI, 0.72–1.25) or levetiracetam (OR, 0.72; 95% CI, 0.43–1.16). Except for ethosuximide, for which the risk estimate must be interpreted cautiously because of the small number of exposures ($n = 61$), the ranking order of different AEDs in terms of MCM risk was similar in the two meta-analyses.

A limitation of meta-analyses is the heterogeneity of data across studies in terms of populations, ascertainment methods, and endpoints. Veroniki's meta-analysis [17], in particular, included studies with different outcome criteria, some studies listing abnormalities that many would not consider MCMs, and excluded data from large prospective registries [2,4,5▪▪,17]. Differences in definitions of MCMs, including methods and time window for their detection, can significantly impact the results [18] which question the validity of comparing MCM frequencies across studies. More meaningful comparisons can be made within individual studies. In this regard, large prospective registries such as the North American Antiepileptic Drugs and Pregnancy Registry (NAAPR), the UK and Ireland Pregnancy Register, and the international EURAP registry have provided useful data [2,4,5▪▪]. The prevalence of MCMs for the eight most frequently used AED monotherapies in NAAPR, the UK and Ireland Register, and EURAP are shown in Fig. 1. In all registries, the highest prevalence of MCMs was associated with valproate, ranging from 6.7 (95% CI, 5.4–8.3%) to 10.3% (95% CI, 8.8–12.0%). The lowest prevalence was associated with lamotrigine, from 1.9 (95% CI, 1.4–2.8%) to 2.9% (95% CI, 2.3–3.7%), and levetiracetam, 0.7 (95% CI, 0.2–2.4%) to 2.8% (1.7–4.5%). The within-registry comparisons between AEDs thus show a consistent pattern. The absolute risk estimates for different AEDs were slightly higher in EURAP than in the other registries (Fig. 1), probably because of EURAP's longer time window (up to one year after birth) for detection of MCMs, which

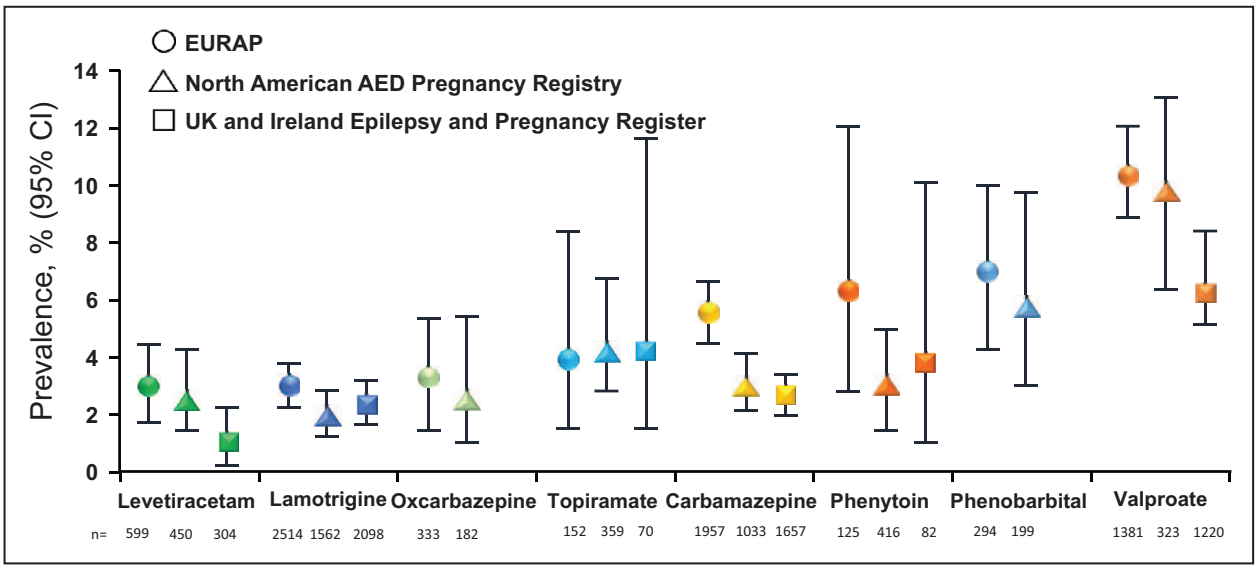

FIGURE 1. Prevalence (%; and 95% confidence intervals, CI) of major congenital malformations with eight different antiepileptic drug monotherapies based on data from three prospective registries [2,4,5▪▪].

highlights the problems in comparing MCM frequencies across studies. EURAP found that for four of the eight AEDs included in the analysis (valproate, phenobarbital, carbamazepine, and lamotrigine), the risk of MCMs increased with increasing dose at time of conception (Fig. 2) [5▪▪]. A dose dependency for the MCM risk has been reported by several other authors for valproate [2,4,19,20] and by another registry for carbamazepine [4]. In the recent EURAP report, the lowest prevalence of MCMs (2.5%; 95% CI, 1.8–3.3%) was associated with lamotrigine up to 325 mg/day [5▪▪]. The study provided ORs for other treatments compared with the lower lamotrigine dose range in a multivariable analysis that included other potential risk factors in addition to type of treatment (Fig. 3). Based on this analysis, oxcarbazepine and levetiracetam were found to be associated with a risk similar to the lower lamotrigine dose. A low risk was also found for phenobarbital 80 mg/day or less, but CIs were wide, and at higher doses phenobarbital was only second to valproate in terms of comparative risk. The AEDs and pregnancy registries include very few pregnancies with exposure to AEDs that are mainly used for nonepilepsy indications such as pregabalin, and direct comparisons between pregabalin and

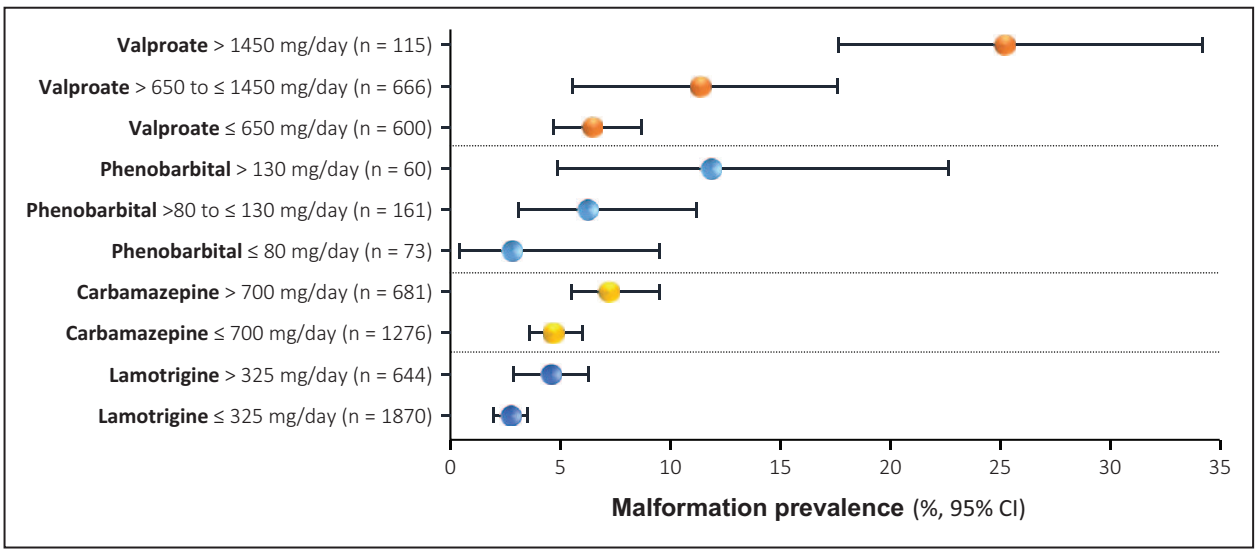

FIGURE 2. Dose dependency of major congenital malformations (%; and 95% confidence intervals) with four antiepileptic drug monotherapies. Based on Data from [5▪▪].

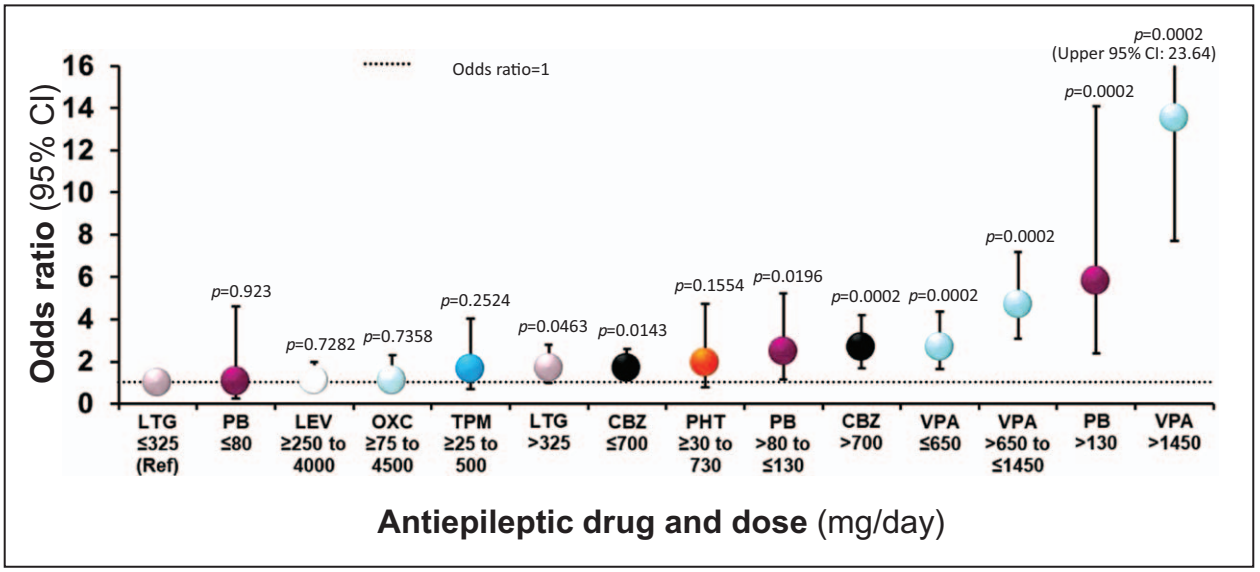

FIGURE 3. Risk of major congenital malformations (odds ratios with 95% confidence intervals) with different antiepileptic drug treatments compared with lamotrigine 325 mg/day or less. CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; Ref, reference; TPM, topiramate; VPA, valproate. Based on Data from [5▪▪].

other AEDs are thus lacking. However, the risk of MCMs associated with pregabalin has recently been compared with that of unexposed children in a cohort study based on the US Medicaid eXtract [21]. Based on 353 pregnancies with monotherapy exposure, pregabalin was not found to be associated with an increased risk of MCMs (adjusted risk ratio 0.87 (95% CI, 0.53–1.42).

Traditionally, MCMs have been considered to occur more frequently with AED polytherapy than with monotherapy [22]. A study based on results from three prospective registries, however, suggests that the type of AEDs included in the polytherapy regimen is more important than whether mono or polytherapy is used [23]. When specific drug combinations were compared, it became clear that inclusion of valproate in the treatment regimen was the main reason for the higher prevalence of MCMs in polytherapy populations. In fact, a recent analysis of EURAP data indicated that addition of lamotrigine to valproate did not increase the teratogenicity risk, and that a low dose of valproate in combination with another AED was associated with lower risks than a higher dose of valproate as monotherapy [24]. In an analysis of 1547 prospective pregnancies from the Kerala registry, an AED was added in the second or third trimester in 143 cases (9.2%) or stopped in 93 (6.0%) [25]. The MCM frequency and Developmental Quotient at one year did not differ between the groups exposed to treatment changes and those with unchanged treatment. These results should be interpreted cautiously given the small numbers and lack of information on reasons for treatment changes.

The growing body of evidence on differences in teratogenic potential between AEDs has had a definite influence on drug selection for women with epilepsy of childbearing age [26]. Changes in AED prescribing patterns during pregnancy over 20 years (1996–2016) were recently analyzed on the basis of 9247 pregnancies from the UK and Ireland Pregnancy Register [27▪]. The study showed a major increase in the use of lamotrigine and levetiracetam and a decrease in valproate and carbamazepine [27▪]. Surprisingly, there was no significant decrease in the prevalence of MCMs although a gradual, nonsignificant reduction was seen. Larger cohorts may be needed to demonstrate improved teratogenic outcomes as result of changes in prescribing pattern.

The AEDs and pregnancy registries and most other cohort studies enroll selected groups of patients, and their results might be affected by selection bias. A few population-based studies have been published in recent years. Data from the Norwegian Medical Birth Registry identified a 3.4% prevalence of MCMs in AED-exposed offspring compared with 2.9% in the general population (OR, 1.27; 95% CI, 1.02–1.59) [10]. In Swedish registries, the MCM prevalence was 6.7% among AED-exposed compared with 4.7% in offspring of mothers with untreated epilepsy (adjusted risk ratio 1.30; 95% CI, 0.95–1.77) [28]. Also, in a population-based study from Italy, the prevalence of MCMs did not differ significantly between AED-exposed (2.3%) and nonexposed newborns (2.0%, OR 1.12; 95% CI,

0.55–2.55%) [29]. Although these findings suggest that the risk associated with AED exposure may be lower than that reported for selected cohorts, the possibility that population-based studies underestimated the risk due suboptimal ascertainment cannot be excluded. In any case, these discrepancies do not invalidate within-cohort comparisons, and differences in risk across AEDs revealed by cohort studies.

COGNITIVE OUTCOMES

Based on 22 prospective cohort and six registry-based studies, a 2014 Cochrane review concluded that prenatal exposure to valproate is associated with reduced intelligence quotient (IQ) in children of a magnitude sufficient to affect education and occupational outcomes in later life [30]. Carbamazepine and lamotrigine appear to be well-tolerated regarding IQ development up to school age, whereas data for other second-generation AEDs is limited or missing [30,31]. A more recent network meta-analysis based on 21 cohort studies confirmed that among AEDs valproate was associated with the greatest risk of adverse cognitive development, with an OR of 7.40 (95% CI, 3.00–18.46) compared with children of untreated women with epilepsy [32].

The single most informative study was the prospective Neurodevelopmental Effects of Antiepileptic Drugs (NEAD study, [6]), which enrolled in early pregnancy women on monotherapy with carbamazepine, lamotrigine, phenytoin and valproate. The primary outcome was the child's IQ at 6 years of age, which was found to be lower after exposure to valproate (mean score 97; 95% CI, 94–101) compared with carbamazepine (105; 95% CI, 102–108), lamotrigine (108; 95% CI, 105–110), or phenytoin (108; 95% CI, 104–112). The difference between treatments was significant only for offspring exposed to valproate doses of at least 1000 mg/day. Verbal performance was the function more affected by valproate exposure [6], and most of the differences were observed already at 3 years of age [33]. A subsequent study, with partly overlapping cohorts of AED-exposed children, also included control children born to mothers with untreated epilepsy and to healthy mothers [7]. The poorer outcomes associated with valproate exposure were confirmed, with an adjusted mean IQ 9.7 points lower (95% CI, 4.9–14.6) for children exposed prenatally to more than 800 mg/day. Although IQ was not reduced in children exposed to less than 800 mg/day, there was evidence of impaired verbal abilities and increased educational needs also at these lower doses. In a preliminary study based on small numbers of children from the UK and Ireland Epilepsy and Pregnancy Register assessed at 5–9 years of age, prenatal exposure to levetiracetam and topiramate was not found to adversely affect cognitive development [34]. In these observational studies, follow-up was not extended beyond 6–9 years of age. However, an analysis of data from the Kerala registry assessed children at 10–12 years. Those exposed *in utero* to phenobarbital had worse cognitive outcomes compared with children exposed to other AEDs, whereas those exposed to valproate had outcomes similar to those of children exposed to carbamazepine or phenytoin [35]. The comparatively favorable outcome with valproate might be explained by the low doses used (mean 480.6 mg/day). In contrast, a recent Danish population-based study showed that, compared with unexposed controls, children exposed prenatally to valproate performed significantly worse than non-exposed children in national language and mathematics tests while attending primary or lower secondary schools [36▪]. No similar association was seen after prenatal exposure to carbamazepine, oxcarbazepine, lamotrigine, or phenobarbital.

BEHAVIORAL OUTCOMES

An analysis of data from the Danish National registries reported that prenatal exposure to valproate was associated with a 4.5% risk of autism spectrum disorder [hazard ratio (HR) 1.7; 95% CI, 0.9–3.2, compared with unexposed controls] and a 2.95% risk of childhood autism (HR 2.9; 95% CI, 1.4–6.0) [8]. There was no indication of dose dependency and no similar association was observed for any other AED. A recent meta-analysis, including five cohort studies, confirmed an increased risk of autism/dyspraxia after valproate exposure [32]. Compared with unexposed controls, the OR for autism/dyspraxia was 17.3 (95% CI, 2.4–217.6). Unlike the Danish study, the meta-analysis found an association between exposure to oxcarbazepine and lamotrigine and autism/dyspraxia. However, the association with oxcarbazepine disappeared when the analysis was restricted to offspring of women with epilepsy and the association with lamotrigine was no longer apparent when only studies of high quality and adequate follow-up were considered [32].

In the NEAD study, children whose mothers took valproate during pregnancy had significantly lower general adaptive composite scores than the lamotrigine and phenytoin groups and were rated by their parents as having more atypical behaviors and inattention than those exposed to lamotrigine or phenytoin. Based upon parent and teacher ratings, children of mothers who took valproate during pregnancy were also at greater risk for a diagnosis of attention-deficit/hyperactivity disorder [37]. Adaptive behavior outcomes were also assessed at 3–6

years of age in a selected sample of children exposed prenatally to valproate, lamotrigine, or carbamazepine from the prospective NAAPR study [38]. The valproate-exposed group was the only group to show adaptive behavior impairments with specific deficits in socialization and motor function. These negative effects were dose-dependent.

In the Norwegian Mother Child cohort study, parents used questionnaires to assess their children at 18 and 36 months of age [39,40▪]. Autistic traits and [40▪] and language delay [39] at 36 months were more common among AED-exposed children ($n = 335$) compared with unexposed children, with adjusted ORs of 7.9 (95% CI, 2.5–24.5) and 4.7 (95% CI, 2.0–10.6), respectively. Folate supplementation from 4 weeks before pregnancy and until the end of the first trimester was associated with a significant reduction in risks [39,40▪].

INTRAUTERINE GROWTH

A population-based study of data from the Danish Medical Birth Registry found that AED-exposed newborns were at increased risk of being small for gestational age (SGA), with an adjusted risk ratio of 1.21 (95% CI, 1.10–1.34) [9]. The highest risk was associated with topiramate, but the risk was significantly elevated also for oxcarbazepine, valproate, clonazepam, and carbamazepine, in decreasing order [9]. A smaller head circumference was reported for primidone, carbamazepine, and valproate, but data on the prevalence of microcephaly were not provided. A similar population-based study of data from the Medical Birth Registry of Norway reported that, compared with unexposed newborns from mothers without epilepsy, those exposed to AEDs had a moderate risk of growth restriction [10]. Remarkably, those exposed to topiramate had an almost five-fold increase in prevalence of microcephaly (11.4 versus 2.4%; OR 4.8; 95% CI 2.5–9.3) and an approximately three-fold increase in prevalence of SGA (24.4 versus 8.9%; OR 3.1; 95% CI, 1.9–5.3) [10]. The risk of growth restriction associated with topiramate was recently confirmed in a report from NAAPR [41]. In the latter study, the prevalence of SGA was increased after exposure to AEDs compared with nonexposure (relative risk, 2.0, 95% CI, 1.3–3.0) and was particularly high (18.5%) for topiramate. An increase in risk of a lesser magnitude was found after exposure to phenobarbital and zonisamide [41].

CONCLUSION

Knowledge on the comparative teratogenic potential of individual AEDs has increased substantially in the last decade. Although most studies have focused on MCMs, it is now clear that adverse effects of prenatal exposure to AEDs extend to growth restriction, cognitive impairment, and behavioral abnormalities. This implies that the vulnerable period may not be restricted to organogenesis but could extend to processes of brain maturation throughout the entire duration of pregnancy.

The risk of adverse fetal effects varies substantially among AEDs and, at least for some AEDs, in relation to the dose used. Studies have consistently found that valproate carries the greatest risk not only for MCMs but also for cognitive and behavioral abnormalities. Awareness of these findings have led to a gradual decrease in its prescription in women of childbearing potential, a trend accelerated by tightened restrictions to its use by regulatory agencies. The decline in the prescription of valproate coincides with an increasing use of some newer generation AEDs. In fact, lamotrigine, levetiracetam, and oxcarbazepine are probably associated with the lowest risk of adverse fetal effects when taken during pregnancy. This is one major positive feature associated with introduction of some second-generation drugs.

Overall, the findings reviewed in this article provide physicians and women with epilepsy with the evidence required to make more rational treatment decisions. Detailed recommendations on the management of epilepsy in girls, women of childbearing potential, and pregnant women are beyond the purpose of this article and are provided in recent publications [11,42].

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Conflicts of interest

There are no conflicts of interest.

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