ILAE report

Epileptic Disord 2019; 21 (6): 497-517

Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy

Torbjörn Tomson [1], Dina Battino [2], Rebecca Bromley [3], Silvia Kochen [4], Kimford Meador [5], Page Pennell [6], Sanjeev V. Thomas [7]

[1] Department of Clinical Neuroscience Karolinska Institutet, and Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
[2] Epilepsy Center, Department of Neurophysiology and Experimental Epileptology, Fondazione IRCCS Istituto Neurologico CARLO BESTA, Milan, Italy
[3] Division of Evolution and Genomic Science, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[4] Epilepsy Center, ENyS, CONICET, Hosp. El Cruce, Hosp. R. Mejía, Univ Buenos Aires, Argentina
[5] Department of Neurology & Neurological Sciences, Stanford University, Palo Alto, CA, USA
[6] Department of Neurology, Harvard Medical School, Divisions of Epilepsy and Women's Health, Brigham and Women's Hospital, Boston, MA, USA
[7] Department of Neurology, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala State, India

Received July 02, 2019; Accepted October 05, 2019

ABSTRACT – The risks associated with use of antiepileptic drugs during pregnancy are a major concern for all women with epilepsy with childbearing potential. These risks have to be balanced against foetal and maternal risks associated with uncontrolled seizures. This report from the International League Against Epilepsy Task Force on Women and Pregnancy aims to provide a summary of relevant data on these risks as a basis for expert opinion recommendations for the management of epilepsy in pregnancy. The report reviews data on maternal and foetal risks associated with seizures as well as teratogenic risks associated with antiepileptic drug exposure, including effects on intrauterine growth, major congenital malformations, and developmental and behavioural outcomes. The impact of pregnancy on seizure control and on the pharmacokinetics of antiepileptic drugs are also discussed. This information is used to discuss how treatment may be optimized before conception and further managed during pregnancy.

Key words: epilepsy, pregnancy, antiepileptic drugs, foetal risks, teratogenesis

Correspondence:
Torbjörn Tomson
Department of Clinical Neuroscience,
Karolinska Institutet,
Department of Neurology,
Karolinska University Hospital,
SE 171 76 Stockholm, Sweden
<torbjorn.tomson@sll.se>

doi:10.1684/epd.2019.1105

It is estimated that, globally, approximately 15 million women with epilepsy are of childbearing age. Most of these women are in need of effective and safe treatment for their epilepsy also during pregnancy. For them, as well as for their partners, the possible risks to the unborn induced by use of antiepileptic drugs (AEDs) during pregnancy is a major concern. While it is important to understand that the vast majority of women with epilepsy can have uneventful pregnancies and give birth to perfectly healthy children, there are also foetal risks associated with treatment. These risks include negative effects on foetal growth, increased risks of major congenital malformations (MCM), as well as adverse effects on neurocognitive and behavioural development. However, uncontrolled maternal seizures can also be harmful not only to the pregnant woman but also to the foetus. The aim of this article is to present the facts on these risks and, most importantly, based on this, to provide practical recommendations on how risks can be balanced and reduced and suggest how epilepsy may be managed before and during pregnancy and after delivery in order to optimize outcomes. The recommendations are based on review of the relevant literature carried out by the International League Against Epilepsy (ILAE) Task Force on Women and Pregnancy. The search strategy and criteria for selection are summarized in *Box 1*.

Box 1. Search strategy.

References for this review were identified from the authors' files and from a PubMed search (from 2009 through August 2019) using at least one of the following terms (by searching as text words): "epilep*", "seizure*", "antiepileptic*", "anti-epileptic*", "anticonvuls*", "anti-convuls*", "barbit*, and specific drug names. Publications found were limited to those retrieved by searching as text word at least one of the following terms: "pregnan*", "maternal", "mother", "parent*", "fetal", "foetal", "fetus", "foetus", "feto*", "foeto*", "defects", "embryopat*", ("congenital" AND "malformation*"), ("congenital" AND "abnormalit*"), ("congenital" AND "anomal*"), "offspring*", "utero", "terato*", "intrauterine", "intra-uterine", ("before" AND "birth"), "infant", "prenatal", "pre-natal", "obstetric*, "delivery", ("birth" AND "outcome*"), ("children" AND "of" AND "women"), and ("pregnancy" AND "cognitive development" OR "development" OR "neurodevelopment" OR "IQ"). Eligible articles were further limited by excluding all the articles found by entering in the medical subject headings field, the expression ("animals" NOT "human"). Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Emphasis was focused on publications in the last 10 years, *i.e*. after the publication of the guidelines from the American Epilepsy Society (Harden *et al*., 2009a, 2009b). Recommendations should be considered as an expert opinion rather than evidence-based guidelines. This approach was taken due to limitations in the present evidence base, which leave clinicians and their patients without adequate information. This report is intended to fill this gap, at least in part.

The manuscript is addressing the following learning objective of the ILAE curriculum (Blümcke *et al*., 2019): "*Provide guidance regarding pregnancy, including teratogenicity of the various antiepileptic drugs*".

To further illustrate the discussion, four brief case vignettes are presented and discussed at the end of the article.

Maternal and foetal risks associated with seizures

The risk of seizures during pregnancy and the consequences that they might have on the developing foetus as well as the mother are fundamental reasons for the use of AEDs, and this should be no different for epileptic women with childbearing potential as they may become pregnant (Sveberg *et al*., 2015).

Focal seizures that do not evolve to bilateral tonic-clonic seizures are unlikely to have a major impact on the foetus, although there are a few case reports indicating brief foetal distress, expressed as deceleration of foetal heart rate for 2.5-3.5 minutes, during focal seizures with impaired awareness (Nei *et al*., 1998; Sahoo and Klein, 2005). Generalized tonic-clonic seizures (GTCS), including focal to bilateral tonic-clonic seizures according to the current classification (Fisher *et al*., 2017), are associated with hypoxia and lactic acidosis, which during pregnancy are transferred to the foetus through the placenta and may lead to asphyxia (Hiilesmaa and Teramo, 2013). Seizure-related falls can also cause blunt trauma to the uterus and thus affect the foetus.

A nation-wide register-based study from Taiwan found an association between the occurrence of seizures of all types during pregnancy and small foetal size for gestational age, moreover, seizures during pregnancy were more likely to be associated with preterm delivery and lower birth weight (Chen *et al*., 2009). In this study, occurrence of seizures was defined as those in women being hospitalized or treated in the emergency department for epilepsy during pregnancy, and no distinction was made between different seizure types. A smaller hospital-based retrospective study from Norway found no differences in obstetrical complications between women with seizures during the last five years, based on medical records (type of seizures not

specified), and those without (Borthen *et al*., 2011). However, differences in methodology make it difficult to compare between the results of these two studies.

There are no indications of an association between maternal seizures and risk of MCM, but one retrospective study has indicated lower verbal IQ in children of mothers with five or more GTCS during pregnancy (Adab *et al*., 2004). The retrospective study design, however, precludes definitive conclusions, and this observation has not been confirmed in prospective studies (Meador *et al*., 2013; Baker *et al*., 2015), although these were not designed to address the question of possible impact of maternal GTCS during pregnancy on the child's neurodevelopment.

Epilepsy and uncontrolled seizures are also associated with maternal risks. Up to a 10-fold increased risk of maternal mortality (Edey *et al*., 2014) or mortality during hospitalised delivery (MacDonald *et al*., 2015) has been reported for women with epilepsy. When the causes of death were analysed, the majority were seizure related and most due to sudden unexpected death in epilepsy (SUDEP) (Edey *et al*., 2014).

Epilepsy is not considered as a reason for Caesarean delivery, unless a seizure occurs during labour, making the patient unable to cooperate (Donaldson, 2002).

- Generalized tonic-clonic seizures are associated with risks to the foetus as well as to the pregnant woman.
- Other seizures are probably less harmful, but may be associated with injury, intrauterine growth retardation and premature delivery.

Teratogenic risks

Effects of antiepileptic drugs on intrauterine growth

The possibility that AED use during pregnancy is associated with offspring that are small for gestational age (SGA) and have small head circumference has been discussed for many years, mainly based on outcomes of selected cohorts of pregnant women with epilepsy (Harden *et al*., 2009b). Particular interest has been paid to the risk of microcephaly as this could be associated with functional deficits. SGA newborns are at risk of stillbirth and other long-term sequelae. Earlier hospital-based cohort studies (Battino *et al*., 1999; Hvas *et al*., 2000) as well as population-based register studies (Wide *et al*., 2000a; Almgren *et al*., 2009; Veiby *et al*., 2009) have indicated an increased risk of small head circumference among children exposed to AED polytherapy or monotherapy with primidone, phenobarbital (Hiilesmaa *et al*., 1981; Battino *et al*., 1999), carbamazepine (Hiilesmaa *et al*., 1981; Wide *et al*., 2000a; Almgren *et al*., 2009; Veiby *et al*., 2009) or valproate (Wide *et al*., 2000a). Although these studies report smaller head circumference among those exposed, they have not shown increased rates of microcephaly. The prospective NEAD study found increased rates of microcephaly (defined as $<3^{rd}$ percentile) with carbamazepine and valproate, but normalization by two years of age (Pennell *et al*., 2012).

For obvious reasons, the impact of the newer-generation AEDs was not assessed in the earlier studies. However, a more recent population-based study from Norway reported that, in general, children exposed to AEDs had a moderate risk of growth restriction. However, compared to children of healthy mothers, those exposed to topiramate had a considerable risk of microcephaly (11.4% *vs*. 2.4 %; *odds ratio* [OR]: 4.8) and SGA (24.4 % *vs*. 8.9 %; OR: 3.1) (Veiby *et al*., 2014). Increased risk of microcephaly (defined as head circumference $<2.5^{th}$ percentile), although to a lesser extent, was also reported to be associated with carbamazepine (OR: 2.0) and AED polytherapy (OR: 2.0). The same study found a significantly increased risk for SGA with carbamazepine (OR: 1.4) and AED polytherapy (OR: 1.6). A Danish population-based study confirmed a more than two-fold increased risk of SGA with topiramate exposure, and a less, but significantly increased, risk associated with valproate and carbamazepine (Kilic *et al*., 2014). Based on a recent population-based Swedish register study, relative to lamotrigine exposure, infants exposed to carbamazepine and valproic acid had head circumference that was smaller by 0.2 SDs, those exposed to levetiracetam had smaller head circumference by 0.1 SD, while pregabalin-exposed infants had the same head circumference as those exposed to lamotrigine (Margulis *et al*., 2019). Other AEDs were not included in the report. Data from the North American Antiepileptic Drug Pregnancy Registry (NAAPR), based on a selected cohort of women with epilepsy, indicated that the prevalence of SGA was increased in infants exposed to AEDs compared with unexposed infants (relative risk [RR]: 2.0, 95% CI), and that the prevalence of SGA was particularly high (18.5%) for topiramate, but also increased with exposure to phenobarbital or zonisamide (Hernandez-Diaz *et al*., 2017).

An association between exposure to an AED and intrauterine growth restriction does not necessarily mean that there is a direct causal relationship. For example, an early study from Finland demonstrated a genetic influence, indicating that head circumference was smaller among fathers of the group of AED-exposed children with small head circumference (Gaily *et al*., 1990).

The most consistent finding in these studies is the growth restriction associated with maternal use of

topiramate. While the potential functional consequences of this remain to be assessed, the findings call for some caution in the use of topiramate during pregnancy when reasonable treatment alternatives are available.

- Treatment with certain AEDs is associated with an increased risk of intrauterine growth restriction.
- The effect on growth varies between different AEDs and appears to be most pronounced with topiramate.

Major congenital malformations

The first reports of an association between AEDs and congenital abnormalities were published more than 50 years ago (Meadow, 1968). Research over the years since 1968 has revealed that AEDs differ in their potential to cause MCMs. Two recent systematic reviews agree that, for monotherapy, the highest risk is associated with valproate and the lowest with lamotrigine and levetiracetam exposure (Weston *et al*., 2016; Veroniki *et al*., 2017). Based on a network meta-analysis (Veroniki *et al*., 2017), the OR for MCM, relative to unexposed patients, was 2.93 for valproate (95% CI: 2.36-3.69), 1.90 for topiramate (95% CI: 1.17-2.97), 1.83 for phenobarbital (95% CI: 1.35-2.47), 1.67 for phenytoin (95% CI: 1.30-2.17), and 1.37 for carbamazepine (95% CI: 1.10-1.71), while no increase was noted with lamotrigine (OR: 0.96; 95% CI: 0.72-1.25) or levetiracetam (OR: 0.72; 95% CI: 0.43-1.16). A Cochrane review (Weston *et al*., 2016) reported similar results. Compared with offspring of women without epilepsy, the RR for valproate was 5.69 (95% CI: 3.33-9.73), topiramate was 3.69 (95% CI: 1.36-10.07), phenobarbital was 2.84 (95% CI: 1.57-5.13), phenytoin was 2.38 (95% CI: 1.12-5.03), and carbamazepine was 2.01 (95% CI: 1.20-3.36). There was no increased risk of MCMs with lamotrigine (Weston *et al*., 2016). Gabapentin, levetiracetam, oxcarbazepine, primidone or zonisamide were not associated with an increased risk, however, there were substantially fewer data for these medications (Weston *et al*., 2016). While meta-analysis is a method to increase statistical power, an important trade-off is the inclusion of data from heterogeneous studies, with different populations and even different criteria for MCMs (Veroniki *et al*., 2017), both of which can significantly impact the results (Tomson *et al*., 2010). A comparison between treatments should therefore ideally be made within individual studies. In this regard, prospective AED and pregnancy registries that have documented pregnancies over 20 years have provided very useful data (Hunt *et al*., 2008; Hernandez-Diaz *et al*., 2012; Mawhinney *et al*., 2013; Campbell *et al*., 2014; Tomson *et al*., 2018). The prevalence of MCMs for the most frequently used AEDs as monotherapy observed in the three major registries, the NAAPR, UK and Ireland Register, and EURAP, are summarized in *table 1*. All three registries confirm the greater risk with valproate and the comparatively low risk with lamotrigine and levetiracetam. Based on the individual pregnancy registries, the risk of MCM was analysed relative to dose. All registries revealed increasing risks with higher doses of valproate, with cut-offs for higher risks ranging from 500 mg/day based on the NAAPR, to 600 mg/day and 650 mg/day based on the UK-Ireland and EURAP registries, respectively. Based on the EURAP, a dose-dependent effect was also identified for carbamazepine, lamotrigine and phenobarbital, whereas the UK-Ireland registry confirmed dose-dependency for carbamazepine (Hernandez-Diaz *et al*., 2012; Campbell *et al*., 2014; Tomson *et al*., 2018). Based on the EURAP, the lowest risk was associated with lamotrigine at $\leq$325 mg/day at conception. In comparison, the prevalence of MCMs was significantly higher at all doses of carbamazepine and valproate. Valproate at doses as low as $\leq$650 mg/day was also associated with an increased risk compared with levetiracetam (OR: 2.43; 95% CI: 1.30-4.55) (Tomson *et al*., 2018).

Polytherapy has traditionally been considered to be associated with a higher risk of MCMs than monotherapy (Harden *et al*., 2009b; Veroniki *et al*., 2017). However, more recent studies indicate that the type of AED included as polytherapy is more important than the number of AEDs. When data from different registries on specific drug combinations were compared, it was clear that inclusion of valproate as polytherapy was the main reason for higher prevalence of MCMs (Morrow *et al*., 2006; Holmes *et al*., 2011). A recent report from the prospective Kerala Registry of Epilepsy and Pregnancy indicates that the excess MCM risk associated with combination therapy with two AEDs (duotherapy) was largely dependent on the inclusion of valproate or topiramate, in combination with one other AED (Keni *et al*., 2018). Based on the prospective EURAP, a comparison of MCM rates relative to valproate monotherapy and duotherapy at different dose levels of valproate revealed that a low dose of valproate given in combination with another AED was associated with lower MCM rates than a higher dose of valproate as monotherapy (Tomson *et al*., 2015).

AEDs also differ according to the type of MCM they are associated with. A pooled analysis of 32 prospective cohort studies revealed a particularly high prevalence of cardiac malformations with barbiturates, and high prevalence of neural tube defects and hypospadia with valproate (Tomson *et al*., 2016), which was confirmed in two recent meta-analyses (Weston *et al*., 2016; Veroniki *et al*., 2017). Topiramate monotherapy has been associated with increased risk of cleft lip/palate (de Jong *et al*., 2016; Veroniki *et al*., 2017,

Table 1. Prevalence (%) of major congenital malformations (malformed/exposed) for different monotherapies. Data from three prospective registers.

Drug	International Registry of Antiepileptic Drugs and Pregnancy (EURAP)		North American AED Pregnancy Registry		UK Epilepsy and Pregnancy Register	
	Prevalence	(95%CIs)	Prevalence	(95%CIs)	Prevalence	(95%CIs)
Carbamazepine	5.5 % (107/1,957)	(4.5 - 6.6)	3.0% (31/1,033)	(2.1 - 4.2)	2.6% (43/1,657)	(1.9 - 3.5)
Lamotrigine	2.9% (74/2,514)	(2.3 - 3.7)	1.9% (31/1,562)	(1.4 - 2.8)	2.3% (49/2,098)	(1.8 - 3.1)
Levetiracetam	2.8% (17/599)	(1.7 - 4.5)	2.4% (11/450)	(1.4 - 4.3)	0.7% (2/304)	(0.2 - 2.4)
Oxcarbazepine	3.0% (10/333)	(1.4 - 5.4)	2.2% (4/182)	(0.9 - 5.5)		
Phenobarbital	6.5% (19/294)	(4.2 - 9.9)	5.5% (11/199)	(3.1 - 9.6)		
Phenytoin	6.4% (8/125)	(2.8 - 12.2)	2.9% (12/416)	(1.7 - 5.0)	3.7% (3/82)	(1.2 - 10.2)
Topiramate	3.9% (6/152)	(1.5 - 8.4)	4.2% (15/359)	(2.5 - 6.8)	4.3% (3/70)	(1.5 - 11.9)
Valproate	10.3 % (142/1,381)	(8.8 - 12.0)	9.3% (30/323)	(6.6 - 12.9)	6.7% (82/1,220)	(5.4 - 8.3)

Blotière *et al*., 2019), a risk that appears to be dose-dependent (Hernandez-Diaz *et al*., 2018). Based on a recent nationwide cohort study utilizing French health care databases, valproate was associated with eight different MCMs, whereas no significant association with any specific MCM was identified for lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, or gabapentin (Blotière *et al*., 2019).

The risk of MCM is also affected by other factors. Based on the EURAP, parental history of MCMs was associated with a three-fold increase in risk (Tomson *et al*., 2018). Earlier studies indicate a high risk of MCMs in the offspring from subsequent pregnancies in women who had previously given birth to a child with MCM, suggesting individual susceptibility or a genetic predisposition (Campbell *et al*., 2013; Vajda *et al*., 2013).

Based on the EURAP, changes in AED prescription were recently reported during pregnancy over a 14-year period (Tomson *et al*., 2019). In parallel with decreased use of valproate and carbamazepine and increased prescription of lamotrigine and levetiracetam, the prevalence of MCMs declined by 27% over the time period.

- Valproate is associated with the highest risk of MCMs, phenobarbital and topiramate with an intermediate risk, and lamotrigine and levetiracetam with the lowest risk.
- The risk of MCMs is dose-dependent for valproate and probably also for other AEDs such as carbamazepine, phenobarbital and lamotrigine
- For polytherapy, the type of AED included is at least as important as the number of AEDs.

Developmental and behavioural outcomes

Both animal and human studies demonstrate that prenatal exposure to valproate adversely affects foetal brain development. Children exposed to valproate *in utero* are at an increased risk of poorer development in infancy (Bromley *et al*., 2010; Veiby *et al*., 2013a) and reduced IQ and other cognitive functions in preschool years (Meador *et al*., 2009; Cohen *et al*., 2011; Meador *et al*., 2011). At school age, IQ is reduced by 7-11 IQ points with abilities falling below average range in 20-40% of valproate-exposed children (Nadebaum *et al*., 2011; Meador *et al*., 2013; Bromley *et al*., 2014; Baker *et al*., 2015). Other key school-aged cognitive skills, such as memory, attention and language skills, have also been found to be poorer in comparison to control children and children exposed to other AEDs (Nadebaum *et al*., 2011; Meador *et al*., 2013; Baker *et al*., 2015; Bromley *et al*., 2016). Not surprisingly, such cognitive deficits have been reported to lead to increased rates of educational intervention, with reported levels of need for 29-48% of exposed children across studies for valproate monotherapy (Adab *et al*., 2001, 2004; Baker *et al*., 2015), with a dose-dependent influence (Baker *et al*., 2015). For children with clinically diagnosed physical features of valproate embryopathy, the need for educational support is much higher, at 74% (Moore *et al*., 2000; Bromley *et al*., 2019). Recent data from the Danish National Birth Cohort has demonstrated poorer educational examination outcomes in late primary and early secondary school (Elkjaer *et al*., 2018) and an increase in learning disabilities (Bech et al., 2018), highlighting the longer term and likely permanent valproate effects on cognition. Additionally,

prenatal exposure to valproate is associated with an increased risk of autistic spectrum disorder diagnoses (Bromley *et al.*, 2013; Christensen *et al.*, 2013), attention deficit hyperactivity disorder (Adab *et al.*, 2004; Cohen *et al.*, 2011; Bromley *et al.*, 2013; Christensen *et al.*, 2019), and other parent-rated behavioural problems (Huber-Mollema *et al*, 2019). These risks are clearly dose related although no dose of valproate has been proven to be devoid of neurodevelopmental risks, and doses of <400 mg/day have been associated with decreased verbal IQ and increased need for educational assistance (Adab *et al.*, 2004; Meador *et al.*, 2009, 2013; Bromley *et al.*, 2014; Baker *et al.*, 2015).

Investigations of foetal carbamazepine exposure and early infant development have highlighted that development levels are comparable overall to expected trajectories for early infant development and school-aged IQ (Bromley *et al.*, 2014). School-age IQ is higher in children with foetal carbamazepine exposure relative to foetal valproate exposure (Adab *et al.*, 2004; Gaily *et al.*, 2004; Meador *et al.*, 2011, 2013), and is comparable to foetal lamotrigine exposure (Meador *et al.*, 2011, 2013) and that of control children (Rihtman *et al.*, 2013; Baker *et al.*, 2015). However, there may be risks associated with reduced verbal reasoning skills (Meador *et al.*, 2014; Baker *et al.*, 2015). Children with foetal carbamazepine exposure were worse at mathematics in sixth grade compared with unexposed controls, but the actual difference was small (Elkjaer *et al.*, 2018). Lower grades are consistent with an earlier study in which a smaller number of children obtaining high-level passes was documented (Forsberg *et al.*, 2011), however, the mechanism through which such an impact on education occurs remains unclear. An earlier association with an increased risk of autistic spectrum disorder among carbamazepine-exposed individuals (Rasalam *et al.*, 2005) has not been replicated by a large national cohort (Christensen *et al.*, 2013) or observational study (Bromley *et al.*, 2013), or based on parental ratings of symptoms of autistic behaviours (Huber-Mollema *et al.,* 2019). Increased behavioural problems have recently been reported in middle childhood (Huber-Mollema *et al*, 2019), however, only 14% of carbamazepine-exposed children reached this clinical threshold which was based on parental ratings.

Children exposed to phenytoin *in utero* do not appear to have poorer early developmental skills in infancy (Wide *et al.*, 2000b; Thomas *et al.*, 2008; Bromley *et al.*, 2014), although this is in contrast to one early study (Scolnik *et al.*, 1994). School-aged cohorts exhibit expected IQ levels (Gaily *et al.*, 1988; Meador *et al.*, 2009), but the data available are limited due to the cohort size exposed to monotherapy. Children exposed *in utero* to phenytoin are reported to have higher IQ than those exposed to valproate and have comparable IQ to groups exposed to carbamazepine or lamotrigine (Meador *et al.*, 2013; Bromley *et al.*, 2014). In terms of specific developmental outcomes, one study highlighted poorer language skills (Rovet *et al.*, 1995) whilst another noted poorer motor development (Wide *et al.*, 2002), however, based on the more recent NEAD study, poorer levels of language or motor functioning were not documented (Meador *et al.*, 2009, 2011, 2013; Cohen *et al.*, 2011, 2019). The relationship between phenytoin dose and poorer neurodevelopmental outcome was investigated, and no dose response was reported (Meador *et al.*, 2013).

Early development of infants exposed *in utero* to lamotrigine has not been found to deviate from expected trajectories (Bromley *et al.*, 2010; Cummings *et al.*, 2011) and has been demonstrated to be superior to children exposed *in utero* to valproate (Meador *et al.*, 2009). At school age, the NEAD study found that children exposed *in utero* to lamotrigine were superior in their IQ, memory and verbal skills compared to foetal valproate exposure (Meador *et al.*, 2013). IQ levels comparable to controls have been demonstrated in two studies, but they were only powered to detect large levels of difference (Rihtman *et al.*, 2013; Baker *et al.*, 2015). Children exposed *in utero* to lamotrigine had comparable mathematics and Danish language examination results relative to control children (Elkjaer *et al.*, 2018). In contrast, the Norwegian MoBa study reported poorer language and social skills at 36 months based on a parental report for children exposed to lamotrigine (Veiby *et al.*, 2013a). This has not been found by others based on direct child assessment (Bromley *et al.*, 2010), however, relative verbal weakness *vs.* non-verbal skills was identified in the NEAD study, although verbal skills were within normal range (Meador *et al.*, 2013). Children exposed to lamotrigine have not been found to be at higher risk of autistic spectrum diagnoses (Bromley *et al.*, 2013; Christensen *et al.*, 2013), but a recent study reported an increase in certain behavioural outcomes (Huber-Mollema *et al.*, 2019), however, a comparison to an unexposed population was not undertaken in this later study.

The available data on the longer-term outcomes of children exposed to levetiracetam *in utero* are provided by a UK study with a small sample size. In this study, the children exposed to levetiracetam did not differ from control children in terms of their early development and performed more strongly than the group exposed to valproate, with the same noted for school-aged IQ (Shallcross *et al.*, 2011, 2014; Bromley *et al.*, 2016). A dose-dependent effect was not observed at any age, but extension of these results into larger prospective cohorts is required. In one study on behavioural outcomes, an increase in certain

behavioural problems was reported for children (mean age: 6.5 years), as rated by parents, (Huber-Mollema *et al*, 2019), however, this requires further investigation as there was no direct comparison to a control group.

Lamotrigine and levetiracetam have become the most commonly used AEDs in pregnancy in tertiary epilepsy centres in the USA (Meador *et al*., 2018) and other countries (Kinney *et al*., 2018). However, data for even these two AEDs are inadequate. The size of cohorts and the outcomes investigated are small, and consideration should be given to the variable relationship between prescribed dose and serum blood levels (Johannessen Landmark *et al*., 2017). Both lamotrigine and levetiracetam exhibit marked changes in metabolism during pregnancy, which can alter foetal exposure, and no study has adjusted for changes in AED blood levels during pregnancy.

Our understanding of the potential impact of other AEDs on the developing brain is almost non-existent. Whilst two studies have investigated topiramate exposure *in utero*, both were small with conflicting findings (Rihtman *et al*., 2012; Bromley *et al*., 2016). For oxcarbazepine, no association with an increased risk of autistic spectrum diagnosis was found (Christensen *et al*., 2013) and examination performance did not differ relative to controls, with the exception of sixth-grade mathematics, although the magnitude of difference was reportedly small (Elkjaer *et al*., 2018). Other studies contained sample sizes that were too small to provide reliable information on other neurodevelopmental outcomes associated with oxcarbazepine. No reliable data are currently available for other AEDs.

Breastfeeding has proven beneficial for both the mother and child (Ip *et al*., 2009). Some have raised concerns over breastfeeding when taking an AED. However, this concern has not been upheld. The NEAD study and a Norwegian study found no adverse neurodevelopmental effects in children at age three years old who were breastfed by mothers on AEDs, and in the NEAD study, children who were breastfed had higher IQ levels at six years of age compared to children of mothers with epilepsy who were not breastfed (Meador *et al*., 2010, 2014; Veiby *et al*., 2013b).

Despite the potential detrimental and lifelong impact on brain development, clear replicated data for the majority of currently prescribed AEDs are lacking. Larger cohorts with investigation of a dose-dependent, or even better, blood concentration-dependent influence on outcomes are required. Care should be taken to ensure that a lack of evidence of harm is not taken as evidence of safety, and risk-benefit discussions with patients about their treatment should reflect what is known and additionally, what is not known, about neurodevelopmental outcomes associated with individual AED treatments.

- Exposure in the womb to valproate carries a significant dose-dependent risk associated with child cognition and neurodevelopmental disorders (*e.g.* autistic spectrum disorder).
- Carbamazepine does not appear to be a major neurobehavioural teratogen.
- Current data regarding lamotrigine suggest comparable IQ to control children.
- There are limited data pertaining to levetiracetam, topiramate and other AEDs in terms of later child cognition.

Seizure control during pregnancy

The seizure burden remains unchanged during pregnancy for about two thirds of women (Thomas *et al*., 2012; Battino *et al*., 2013). In the prospective observational EURAP study, 67% of women were seizure-free throughout pregnancy (Battino *et al*., 2013). The period of pregnancy with the highest incidence of seizures is labour and delivery, but this occurs in no more than 1-2% of pregnancies in women with epilepsy (Battino *et al*., 2013).

The occurrence of seizures before pregnancy is the most important predictor of seizures during pregnancy (Thomas *et al*., 2012). Women who experienced seizures in the month prior to pregnancy had a 15-fold greater risk of seizures during pregnancy (Thomas *et al*., 2012). Conversely, more than 80% of women who were seizure-free the year before conception, remained so throughout pregnancy (Vajda *et al*., 2008). The impact of a specific pattern of seizures before pregnancy on the course during pregnancy has been investigated in a prospective follow-up of seizure course in women with catamenial epilepsy and women with non-catamenial epilepsy (Cagnetti *et al*., 2014). Seizure control was improved during pregnancy in the catamenial group; 44.1% experienced a ≥50% reduction in seizures, whereas only 6.5% of those with non-catamenial epilepsy had a similar reduction in seizures.

Other general predictors of seizure worsening during pregnancy are focal epilepsy syndromes, the need for polytherapy, and decreased serum levels of AEDs compared to preconception baseline (Reisinger *et al*., 2013). The clearance of newer AEDs, such as lamotrigine, levetiracetam, and oxcarbazepine, is increased significantly during pregnancy which may result in break-through seizures related to lower serum levels if dosages are not adjusted (Pennell *et al*., 2008; Voinescu

et al., 2018). This is discussed in more detail in the following section.

Other factors that may predispose to seizure aggravation during pregnancy include anxiety, non-adherence to medication, sleep deprivation, and difficulty in retaining orally administered AEDs due to vomiting.

Appropriate counselling can help to alleviate the stress factors and improve drug therapy adherence, which is in line with the observation that women with planned pregnancies have a lower frequency of seizures during pregnancy (Abe *et al.*, 2014).

Status epilepticus was reported in only 0.6% of all pregnancies in the EURAP study (Battino *et al.*, 2013); of these, 10 were convulsive, and cases were evenly distributed over the three trimesters. Perinatal death occurred in one of the pregnancies of women experiencing a convulsive status epilepticus, and none of the mothers died.

- Most women with epilepsy maintain their seizure control during pregnancy.
- Pre-pregnancy seizure control is the most important predictor of seizure control during pregnancy.
- Non-adherence to AED medication and alterations in AED clearance are major causes of break-through seizures.

Pharmacokinetic changes during pregnancy

A challenge in managing epilepsy during pregnancy is the pronounced pharmacokinetic alterations, including altered absorption, increased volume of distribution, elevated renal excretion, and induction of hepatic metabolism. AED clearance is a term that can account for all these changes, and is calculated as follows:

Clearance = AED dose (mg/kg/day) / AED concentration

Knowledge about the pattern of gestational age-dependent clearance changes can help guide the timing and range of AED dose adjustments and contribute to maintaining seizure stability during pregnancy.

Lamotrigine is the most studied AED with regards to clearance changes during pregnancy, with findings of markedly increased clearance during pregnancy (Pennell *et al.*, 2008; Harden *et al.*, 2009a; Pennell, 2013; Tomson *et al.*, 2013), likely mainly due to oestrogen-driven enhanced glucuronidation during pregnancy. Additionally, substantial inter-individual variability was noted in most of these studies. A formal pharmacokinetic modelling analysis demonstrated two subpopulations, one with 23% of women who had only a 20% increase in lamotrigine clearance and another with 77% of women who had a 220% increase in clearance, hypothesized to be due to pharmacogenetic differences (Polepally *et al.*, 2014). A recent study with frequent sampling, beginning prior to pregnancy and through the first trimester, highlighted that clearance changes are measurable as early as the third week after conception and clearance increases by an average of 50% by the end of the first trimester (Karanam *et al.*, 2018). These findings underscore the importance of performing therapeutic drug monitoring when available and beginning early in pregnancy.

Studies of other AEDs have demonstrated changes in clearance during pregnancy which vary according to the pathway of drug elimination (*table 2*). For example, early and substantial glomerular filtration rate and renal blood flow increase during pregnancy as well as studies on levetiracetam have demonstrated similar changes in clearance (Tomson *et al.*, 2007; Westin *et al.*, 2008; Lopez-Fraile *et al.*, 2009). A larger and prospective study demonstrated that the increase in clearance is maximal in the first trimester, with a 71% increase above non-pregnant baseline (n=18 pregnancies) (Voinescu *et al.*, 2018). In contrast, studies on carbamazepine report little change in total carbamazepine clearance during pregnancy and no significant change in free carbamazepine or free carbamazepine-10, 11-epoxide concentrations (Johnson *et al.*, 2014).

The clinical importance of the changes in AED clearance has been demonstrated in a few studies. In one early study with lamotrigine (Pennell *et al.*, 2008); pre-conception clinical data were used to determine an individualized target concentration; the ratio-to-target concentration (RTC) was calculated for each blood draw during pregnancy and an RTC threshold of 0.65 was identified as a significant predictor of seizure worsening in the second trimester. Two other studies have reported that this same rule applies to other AEDs, demonstrating that when the AED concentration decreases to 65% or less of the individual target concentration, the risk of seizure worsening increases (Harden *et al.*, 2009a; Reisinger *et al.*, 2013; Voinescu *et al.*, 2018).

During the postpartum period, AED clearances return to non-pregnant baseline, but studies delineating the rate of these changes are limited. An empiric taper of lamotrigine over 10 days to pre-pregnancy baseline plus 50 mg resulted in low rates of lamotrigine side effects and seizure worsening (Pennell *et al.*, 2008). However, based on the only formal pharmacokinetic modelling study of lamotrigine to date, clearance was reported at non-pregnant baseline level over three weeks (Polepally *et al.*, 2014).

Table 2. Summary of individual antiepileptic drug projected decreases in serum concentrations (if no dose changes are made).

AED	Decrease in serum concentration	Decrease in serum free (unbound) concentration	Recommendations to perform therapeutic drug monitoring, if available
Phenobarbital	Up to 55%	Up to 50%	Yes
Phenytoin	60 - 70%	20 - 40%	Yes, free concentration
Carbamazepine	0 - 12%	None	Optional
Valproate	Up to 23%	None	Optional, free concentration if done
Oxcarbazepine monohydroxy-derivative (MHD)	36 - 62%	N/A	Yes
Lamotrigine	0.77 of population: 69% decrease 0.23 of population: 17% decrease	N/A	Yes
Gabapentin	Insufficient data	N/A	Yes
Topiramate	Up to 30%	N/A	Yes
Levetiracetam	40 - 60%, with maximal decrease reached in first trimester	N/A	Yes
Zonisamide	Up to 35% but little data	N/A	Yes

N/A: not applicable.

- Pregnancy can have a major impact on the pharmacokinetics of antiepileptic drugs.
- The most marked decline in serum concentration during pregnancy is seen with lamotrigine, levetiracetam, and oxcarbazepine, but phenobarbital, phenytoin, topiramate, and zonisamide also undergo a clinically relevant increase in elimination.
- A decline in serum concentration by >35% from a pre-pregnancy optimal concentration is associated with increased risk of deterioration in seizure control.
- The extent to which pregnancy affects AED blood levels varies between individual women and is best controlled by blood level sampling.

Optimal management before pregnancy

Preconception care

Preconception care and planning the pregnancy ahead can help to improve the outcome of pregnancy in women with epilepsy. In a study from the UK, women who had proactive counselling prior to pregnancy were more likely to be on monotherapy and on AEDs other than valproate, and the prevalence of MCM in their offspring was lower (Betts and Fox, 1999). Preconception planning and care has also been shown to be associated with improved seizure control and reduced AED burden during pregnancy (Abe *et al*., 2014). Surveys among women with epilepsy who were considering pregnancy revealed that they did not receive sufficient information on pregnancy and epilepsy (Crawford and Hudson, 2003; McGrath *et al*., 2014). One major challenge in provision of adequate pre-conception counselling is unplanned pregnancies. In a recent study from the US, approximately 65% of pregnancies in women with epilepsy were unplanned (Herzog *et al*., 2017). The importance of planning the pregnancy should therefore be brought up regularly in each routine consultation with women with epilepsy with childbearing potential.

The standards of preconception care for women with epilepsy have been discussed and reviewed in the past (Kinney and Morrow, 2016). A protocol for preconception care is provided in *table 3*. This is the period in

Table 3. Recommended management strategies during pre-pregnancy, pregnancy, delivery, and early postpartum.

Timeline	Preconception	Pregnancy 1st trimester	Pregnancy 2nd trimester	Pregnancy 3rd trimester	Postpartum (approximately 6 weeks)
Clinic visits with the neurologist, with discussion topics	**1.** Review the history, imaging and EEG findings to confirm diagnosis and ascertain the epilepsy syndrome **2.** Balance seizure risks against AED risks, by type of AED and dose of AED (*e.g.* MCM, adverse neonatal outcomes, adverse neurodevelopment). **3.** Valproate should be avoided whenever possible. If on valproate, consider whether all other appropriate options have been tried. **4.** Consider whether the patient could be on monotherapy with lower dosage. Consider AED withdrawal if appropriate (epilepsy in remission and high likelihood of successful withdrawal). **5.** Seizure control before pregnancy is important if possible. Counsel the patient about risks of increased seizure rates or severity during a pregnancy, especially if AEDs are stopped abruptly (*e.g.* blunt trauma with risk of foetal loss, injury, or abruptio placentae, decreased foetal oxygenation, increased foetal distress, maternal SUDEP). **6.** Given the incidence of unplanned pregnancies, women with childbearing potential taking AEDs should also be on supplementary folic acid prior to pregnancy and continue throughout pregnancy. See text for discussion of dose.	**1.** Reinforce AED clearance changes and begin AED level monitoring immediately*, if on an AED with substantial clearance changes (*table 2*). **2.** AED dose adjustments for increased seizures or side effects and to maintain baseline, non-pregnant AED level(s)*. **3.** Re-dose AEDs if emesis occurs shortly after AED intake. **4.** Screening for depression and anxiety.	**1.** Continue to monitor changes in AED levels at least monthly*. **2.** AED dose adjustments to maintain baseline level(s)*, and for seizures or side effects. **3.** Review results from prenatal screening tests. **4.** History and neurological examination for signs of increased medication side effects. **5.** Screening for depression and anxiety.	**1.** Possible increased risk of seizure worsening peripartum. **2.** Birth plan recommendations from neurology perspective. **3.** Desire to breastfeed with data to support that benefits outweigh theoretical risks. **4.** Strategies to breastfeed but allow some sleep for the mother. **5.** Postpartum AED taper plan (usually determined after an AED level at 34-37 weeks GA). **6.** Newborn safety and signs for adequate hydration and nutrition if breastfeeding. **7.** History and neurological examination for signs of increased medication side effects. **8.** Screening for depression and anxiety.	**1.** Review history of postpartum seizures and/or medication side effects. **2.** Assess for postpartum depression and anxiety. **3.** Assess sleep hygiene and strategies to increase if needed. **4.** History of infant feeding, growth and development. **5.** Neurological examination for signs of medication side effects.

Table 3. Recommended management strategies during pre-pregnancy, pregnancy, delivery, and early postpartum. (*Continued*).

Timeline	**Preconception**	**Pregnancy 1st trimester**	**Pregnancy 2nd trimester**	**Pregnancy 3rd trimester**	**Postpartum (approximately 6 weeks)**
Blood workup for AED levels, if on an AED with clearance changes during pregnancy (*table 2*)*	Determine optimal individualized baseline pre-pregnancy AED level*.	Monthly AED blood levels*.	Monthly AED blood levels*.	Monthly AED blood levels*.	AED blood level if clinically indicated*.
Communication with the patient about AED dosing		Adjustment of AED dosing for seizures or side effects and to maintain baseline, non-pregnant AED levels.	Adjustment of AED dosing for seizures or side effects and to maintain baseline, non-pregnant AED levels.	Adjustment of AED dosing for seizures or side effects and to maintain baseline, non-pregnant AED levels.	Review if postpartum AED taper was followed and adjust further as needed clinically.
Communication between the neurologist and obstetrician	**1.** Decision on contraception choice/initiation/discontinuation. **2.** Further adjustment of AED regimen regarding type of AED and dose of AED with lowest foetal risk without compromising seizure control.	**1.** Obtain AED levels* (blood can be drawn at more frequent obstetric appointments).	**1.** Obtain AED levels*. **2.** Results from screening tests (blood and ultrasound) reviewed and communicated to patient.	**1.** Obtain AED levels*. **2.** Coordinate labour and delivery hospital care plan with the obstetrician, neurologist, and patient. Include neonatologist for clinical concerns based on prenatal testing.	Neurologist and obstetrician together: **1.** Develop short-term and long-term plan for contraception. **2.** Discuss future pregnancy plans and preferred timing.

*In clinical practice settings with resources to obtain AED blood levels.

which to reconsider the indication for, and the choice of AED treatment. If a change in medication is considered, it should be completed early enough to allow sufficient time to assess the effectiveness of the new regime before conception. This could mean that an attempt to change may need to be initiated as early as one year before a planned pregnancy. The objective of the treatment review and possible revision is to establish, before conception, the lowest effective dose of the appropriate AED for an individual woman, and to document the associated drug serum concentration, when possible.

Folate

It is also important that adequate folate supplementation is initiated in the preconception stage. The US regulatory authorities recommend 0.4 mg of folic acid for all women with child bearing potential and a higher dose of 4 mg daily for women with a higher risk, such as those with past pregnancies involving neural tube defect or anencephaly (Centers for Disease Control, 1992). A higher dose of folate at 4 mg was associated with a lower risk of recurrent neural tube defects based on a randomized controlled trial, in which women with epilepsy were excluded (MRC Vitamin Study Research Group, 1991). In the general population, folate supplementation has been associated with reduced cardiac malformations (Czeizel *et al*., 2013). There are also several studies in the general population showing positive effects of folate supplementation on neurodevelopmental and behavioural outcomes, but this effect remains controversial (Wehby and Murray, 2008; Julvez *et al*., 2009; Roza *et al*., 2010; Schlotz *et al*., 2010; Roth *et al*., 2011; Chatzi *et al*., 2012; Skorka *et al*., 2012; Villamor *et al*., 2012). Despite the fact that some AEDs interfere with folate, data on the effects of folate supplementation on pregnancy outcomes in women treated for epilepsy are not conclusive. Reports from the prospective epilepsy pregnancy registries have failed to demonstrate that periconceptional use of folate is associated with a lower risk of MCMs (Morrow *et al*., 2009; Tomson *et al*., 2018). The NEAD study found improved IQ scores in six-year-old children of women with epilepsy who began folate prior to conception and in early pregnancy (Meador *et al*., 2013). In a related UK study, folate supplementation was not found to be associated with increased IQ scores (Baker *et al*., 2015). In the Norwegian MoBa study, folate supplementation and higher plasma concentration of folate early in pregnancy were associated with a reduced risk of autism symptoms at three years of age in children of women taking AEDs, as rated by the mothers (Bjork *et al*., 2018). Further, data from the Norwegian MoBa study also highlighted a reduction in language delay in children receiving folate supplementation in comparison to those not taking folate (Husebye *et al*., 2018). It should be noted that the observational cohort studies (Morrow *et al*., 2009; Meador *et al*., 2013; Baker *et al*., 2015; Tomson *et al*., 2018) were not primarily designed to assess the effects of folate supplementation. Hence, presence or absence of an association does not prove or exclude a beneficial effect of folate supplementation on AED-induced adverse pregnancy outcomes. Unfortunately, the available data from women with epilepsy provide limited guidance regarding adequate dose of folate. Clearly, women with epilepsy should be prescribed at least 0.4 mg/day since this is the recommended dose for women in general, as well as women with epilepsy according to some guidelines (Harden *et al*., 2009a). The fact that some AEDs can interfere with folate suggests that higher doses of folate might be required, but there have been concerns that folate, in particular at high dose, may increase the risk of cancer, cognitive impairment, and oral clefts (Frankenburg, 2009; Rozendaal *et al*., 2013; Morris *et al*., 2010; Murray *et al*., 2018). Some guidelines recommended that all women with epilepsy who are trying for pregnancy should start on folic acid at 5 mg daily, at least three months prior to pregnancy, and continue with the same dose throughout pregnancy (Wilson *et al*., 2007; NICE, 2012), however, evidence for an optimal periconceptional dose of folate in women with epilepsy taking AEDs remains inadequate. Given the incidence of unplanned pregnancies, women with childbearing potential taking AEDs should also be on folate, at least 0.4 mg/day.

Optimal management during pregnancy, delivery and postpartum

For recommended management strategies during pregnancy, delivery, and early postpartum, see *table 3*. Once pregnancy occurs, it is important to quickly establish detailed coordinated care between the neurologist, obstetrician, and the patient. Since such a large percentage of women will have unplanned pregnancies, the first visit often needs to incorporate elements of preconception care, if not already done so. Regardless, it is ideal to schedule the first pregnancy visit early within the first trimester to ensure that supplementary folic acid is being taken. The physician should re-evaluate the AED dose if not done recently. Counselling of the patient should reinforce the need for AEDs, and any potential AED risk to the foetus should be balanced against the risk of increased seizures to both the mother and the developing foetus (see *Maternal and foetal risks associated with seizures*). If the woman is taking an AED that undergoes substantial clearance changes (*table 2*) and if drug levels are obtainable, it is ideal to determine a blood level

by the mid first trimester given the early gestational changes during clearance that occur for many of the common AEDs used during pregnancy (Karanam *et al*., 2018; Voinescu *et al*., 2018). The individualized target concentration should be reassessed and maintained during pregnancy with blood levels throughout pregnancy (Harden *et al*., 2009a). The need for follow-up drug level monitoring will depend on the type of AED (less important for some AEDs with minor changes during pregnancy, see *table 2*) as well as each woman's sensitivity to alterations in drug levels before pregnancy and her type of epilepsy. Many experts in the field obtain levels every four weeks for AEDs when major changes occur (*e.g.* for lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, and zonisamide), with additional checks if clinically indicated by seizure frequency changes or medication side effects or concerns about medication adherence. The goal is to adjust the AED dosing to maintain the specific target concentration(s) for each woman with epilepsy, given that the risk of seizure worsening increases if the level decreases by 35% or more from the baseline, non-pregnant target concentration (Pennell *et al*., 2008; Reisinger *et al*., 2013; Voinescu *et al*., 2018).

If AED blood levels are not available, then it is reasonable to consider an increase in dose after the first trimester, at least in women whose epilepsy includes GTCS, that were sensitive to changes in AED levels before pregnancy, and who entered pregnancy on the lowest effective dose of their medication, *providing* they are treated with AEDs that are known to undergo marked changes during clearance (lamotrigine, levetiracetam, and oxcarbazepine). There is no evidence to guide how this should be done best, and the issue is further complicated by the fact that the timing and extent to which AED levels decline varies considerably between women. A precautionary approach would be to increase the dose by 30-50%, which in most cases is less than required to maintain the target concentration, while avoiding exposure of the foetus to unnecessarily high AED levels in the few mothers whose serum levels decline less on average. If a woman has a break-through GTCS, a dose increase should be strongly considered, especially if convulsions were previously controlled and if the woman is taking an AED with known marked clearance changes during pregnancy. An increase in other kinds of seizures (*e.g.* focal aware seizures, focal impaired awareness seizures, or JME myoclonic seizures) should also prompt consideration of dose increase.

If the woman is experiencing nausea and emesis, counselling should include strategies to re-dose if emesis occurs shortly after ingestion of her dose. It can be helpful to communicate with the obstetrician for recommendations to reduce emesis if it is interfering with maintaining AED steady-state concentrations.

Patients with epilepsy have higher rates of depression and anxiety than the general population, and this is also the case during pregnancy and the postpartum period. Studies have indicated especially higher rates of postpartum depression in women with epilepsy, and these symptoms often begin intrapartum (Turner *et al*., 2006; Galanti *et al*., 2009). Ideally, management of women with epilepsy should incorporate screening for depression and anxiety, especially during pregnancy and postpartum.

In settings where prenatal testing is available and acceptable, usual testing for all women will include first-trimester Down syndrome screening in the late first trimester, between 9-14 weeks gestational age, with combined measurements of serum beta-hCG and serum pregnancy associated plasma protein (PAPP-A), an ultrasound measurement of nuchal translucency, and consideration of maternal age to provide patient-specific risk (Pennell and McElrath, 2019). These tests also provide confirmation of gestational age and the potential to detect some severe MCMs early. However, a more definitive structural ultrasound will be performed at 18-22 weeks of gestation; in women with epilepsy, it is ideal to obtain a detailed (specialized) foetal structural survey by a trained specialist. Foetal echocardiography is not necessary as a routine measure, but only if there is a clinical indication. If there is a concern for intra-uterine growth retardation, then serial ultrasounds may be performed.

The third trimester is a critical time to coordinate recommendations for labour and delivery and early postpartum care between the neurologist and obstetrician, with consideration of the patient's desired birth plan. If prenatal screening has indicated anticipated newborn problems, the neonatology team should also be included in the planning phase. The diagnosis of epilepsy itself is not an indication for Caesarean section. Seizures and their treatment during labour and delivery may interfere with the patient's ability to participate in active labour, however, this occurs only rarely. Seizures during labour and delivery are best treated with the usual rescue therapy using a low dose of a quick-acting benzodiazepine. Vaginal deliveries are the norm. The benefits of pain management with epidural anaesthesia are the same for women with epilepsy as for any other women, and include reducing the duration of intense pain and maximal stress, and facilitating some rest prior to the active stage of labour. At delivery, all children should routinely receive 1 mg vitamin K IM.

Discussion during the late third trimester should also include possible increased seizure worsening peripartum, desires and strategies for breastfeeding, strategies to lessen prolonged sleep deprivation, newborn safety, and a plan to adjust AED dosing post-

partum if increases have been made during pregnancy (Voinescu and Pennell, 2017).

If AED dosing has been increased during pregnancy, the rate of taper of AEDs back to pre-pregnancy dose or slightly above depends mainly on the primary route of elimination for each individual AED. The physiological changes of renal and some hepatic enzymatic functions (*e.g*. glucuronidation) associated with pregnancy will rapidly resolve over the first two to three weeks postpartum, while other hepatic enzymes (many of the cytochrome P450 enzymes) may take one to two months to return to baseline clearance rates (Yerby *et al*., 1990, 1992). Postpartum AED tapers are prescribed empirically, as a steady-state level is not obtainable with the rapid changes during clearance, and it often takes a few days to obtain results for most of the second- and third-generation AEDs at most clinical centres (see section on *Pharmacokinetic changes during pregnancy*).

Given the benefits of breastfeeding with regards to both short- and long-term neonatal health in the general population (http://www.who.int/topics/breastfeeding/en/), and the data from studies showing no adverse neuropsychological effects in children of mothers taking AEDs, breastfeeding should in general be encouraged. Treatment should be adapted according to how sensitive their seizures are to sleep deprivation based upon their history and their epilepsy syndrome. However, the risk of seizures in the postpartum period relative to specific sleep patterns has not been addressed in high-quality studies.

The risk of seizures may be increased in the postpartum period, sometimes for several months, due to sleep deprivation. Couples and other family members should be counselled, ideally as a function of prenatal care, to make arrangements in order to allow adequate sleep while caring for a newborn. Some families adopt a "shift" approach so the mother can reliably obtain uninterrupted and regular nightly sleep. Additionally, even if the mother has been seizure-free for a long time, she should take a more conservative safety approach until she achieves regular sleep again, given that sleep deprivation is a strong provoker of many seizure types.

Common sense safety considerations during the newborn period should be discussed and reinforced; these include no driving, no bathing of the baby with the mother alone, and no co-sleeping with the mother in the parents' bed. If the mother is at risk of myoclonic seizures, then a baby carrier (sling or harness) should be used when walking around with the baby. In the early postpartum period, the mother should also be discouraged from taking a bath by herself behind a closed, locked door or when no other adult is around.

Conclusions

The challenge in the management of epilepsy during pregnancy is to balance the foetal and maternal risks associated with seizures against the teratogenic risks associated with exposure to AEDs *in utero*. Addressing issues related to pregnancy should begin well before conception in order to maximize pregnancy outcomes. It is clear that AEDs differ in their teratogenic potential. Valproate is associated with the greatest risk of malformations as well as adverse cognitive and behavioural outcomes, and should, whenever possible, be avoided for the treatment of patients who may become pregnant. Lamotrigine and levetiracetam are associated with the lowest risk of malformations, but data on neurodevelopment for levetiracetam is based on a small sample and evidence on the effects of prenatal exposure on neurodevelopment is lacking or insufficient for other newer-generation AEDs. Teratogenic risks should be considered at the time of initiation of AED treatment in young female patients. Pre-pregnancy counselling is essential to ensure that the woman enters pregnancy on the most appropriate AED treatment, taking efficacy as well as foetal safety into account, and that she is also taking folate supplementation. Once pregnancy is established, close monitoring is warranted and ideally in collaboration between epilepsy and obstetric care.

It should finally be emphasized that the vast majority of women with epilepsy will have uneventful pregnancies and give birth to healthy children. The aim of the recommendations in this review is to further facilitate such positive pregnancy outcomes.

Case studies and discussion

Case 1

Christina is 27 years old. She has had epilepsy for two years with focal seizures with impaired awareness; before she was started on treatment, she had had a single focal to bilateral tonic-clonic seizure. MRI was negative. She was initiated on lamotrigine and became seizure-free a year ago after a gradual increase in the lamotrigine dose to 250 mg/day. She is considering pregnancy.

Case 2

Sara is 18 years old with newly diagnosed juvenile myoclonic epilepsy. She first sought medical advice after her second tonic-clonic seizure. Her first seizure occurred after a party night whereas the second seemed unprovoked. In retrospect, it is clear that she has had myoclonic seizures every month for a year.

Case 3

Judy is a 25-year-old woman who has had juvenile myoclonic epilepsy for seven years. The first medication that she tried was levetiracetam. She continued to have tonic-clonic seizures at a dose of 1,500 mg/day. Higher doses induced intolerable psychiatric side effects. She was therefore switched to valproate five years ago and became seizure-free when the dose was increased to 900 mg/day. She has now discovered that she is pregnant at Gestational Week 7, which was unplanned.

Case 4

Miranda is a 25-year-old woman who has juvenile myoclonic epilepsy which was diagnosed at the age of 16. She was first tried on lamotrigine but continued to have tonic-clonic seizures despite a maximum tolerated dose of 400 mg/day. Levetiracetam was added to lamotrigine but seizures continued. Lamotrigine was tapered while the levetiracetam dose was increased gradually up to 3,000 mg/day, a dose at which she experienced intolerable mood changes and continued seizures. Having failed two different drugs at the highest tolerable doses, she was switched from levetiracetam to valproate. She continued to have occasional tonic-clonic seizures until the dose was increased to 800 mg/day (400 mg BID), after which she has been seizure-free for the last three years. She has a boyfriend but no immediate plans to become pregnant.

Cases related to preconception management

In the first case, Christina has focal impaired awareness seizures and rare bilateral tonic-clonic seizures that had responded well to a moderate dose of lamotrigine. The pre-conception care in this instance would focus more on optimal AED usage to maintain seizure freedom during pregnancy and minimise the risk of foetal complications. Ascertaining the blood level of lamotrigine in the preconception stage and instituting folate supplementation at this stage are part of the pre-conception care.

The second case, Sara is in a situation where initiation of AED treatment is justified. Given that she is likely to continue with her treatment for many years, the efficacy as well as the teratogenic potential needs to be considered when deciding on her treatment. While valproate is likely to be the most effective AED for her epilepsy, this drug should be avoided whenever possible in this patient population. The most reasonable first-line options are therefore levetiracetam or lamotrigine. Where available, a trough serum concentration should be obtained prior to pregnancy to establish her target concentration; this concentration should be maintained during pregnancy, and a decrease by 35% or more should be avoided in order to reduce the risk of seizure worsening.

The fourth case, Miranda, is on treatment with valproate after having failed on two other AEDs as monotherapy as well as one combination treatment. Given the known risks to the foetus associated with exposure to valproate, regulators have issued restriction on its use in women with childbearing potential. According to the FDA, valproate should not be administered to a woman with childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable. In such situations, effective contraception should be used (FDA, 2017). The European Medicines Agency (EMA) considers valproate contraindicated in women with childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (European Medicines and Agency, 2018). The latter is a detailed list of requirements, including effective contraception, but also includes a key element relating to information for the woman on the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks.

Miranda should be informed that her current medication is associated with a 7-10% risk of MCM in the offspring as well as a significant risk of reduced IQ (*e.g.* 7-10 IQ points) and other cognitive and behavioural (*e.g.* five-fold increased risk of autism) impairments, should she become pregnant on valproate. The risk of poorly controlled epilepsy needs to be balanced against teratogenic risks associated with valproate.

Another element in the pregnancy prevention programme is to make sure that the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued since valproate is considered contraindicated in pregnancy unless there is no suitable alternative treatment (European Medicines and Agency, 2018).

A major concern has been inadequate informed consent for many women on valproate. Miranda needs detailed current information on the risks and potential benefits of all possible treatment options in order to make a shared informed decision. Depending on her personal situation, she might prefer not to risk loss of seizure control with treatment changes right now, or at all, or she could opt for such changes as soon as possible. Regardless, she should be recommended folate supplementation. The EMA recommends dividing the valproate daily dose into several doses over a day and/or use of extended release formulations if valproate is going to be used during pregnancy, but there are no clinical data showing that

this approach reduces teratogenic risks (Mawhinney *et al.*, 2012).

Half of pregnancies are not planned, thus scheduling discussion once a pregnancy is planned will be too late for many pregnancies. Women should be informed of risk at the time of valproate prescription. Given the risk of unplanned pregnancy, Miranda may prefer to consider treatment alternatives at this stage. She has already failed the two most reasonable alternatives, and also tried the lowest effective dose of valproate. Therefore, established suitable alternatives have been tried without acceptable seizure control. Other possible alternatives beyond lamotrigine and levetiracetam include zonisamide and topiramate. Both have limited documentation regarding effectiveness for JME, as well as safety in pregnancy. While the limited data on zonisamide do not signal an increased risk of MCMs, no data on the effects of foetal zonisamide exposure on neurodevelopment are available. Topiramate appears to be associated with an intermediate risk of MCMs (about 4.5%), and limited data in animals and humans suggest that it does not have major neurodevelopmental effects. There are essentially no data on pregnancy safety for other AEDs which are effective for generalized epilepsy (e.*g.* perampanel). If valproate cannot be avoided, one option may be to consider a decrease in valproate with addition of lamotrigine.

Case related to management during pregnancy

Considering our third case, Judy is already pregnant. The data discussed in previous sections highlight that there are increased risks regarding aspects of neurodevelopment and physical malformations associated with valproate treatment. Most of the period when malformations are more likely to occur has already passed, and treatment modification will not reduce these risks. However, in contrast, valproate exposure throughout pregnancy may have an impact on neurodevelopment. Importantly, these adverse effects have been found to be dose-dependent. Her dose of 900 mg/d is on the low side, with the evidence to date demonstrating increased risks over 800-1,000 mg/d, but there are still risks noted at doses <800 mg/d (Baker *et al.*, 2015). Switching her AED during pregnancy will lead to a period of polytherapy. If an attempt is made to switch to lamotrigine, the transition period with polytherapy may require 7-8 weeks in order to minimize the risk of idiosyncratic reactions. Given Judy's previous trial of other AEDs, a switch from, or withdrawal of valproate may lead to suboptimal control of her epilepsy. It is therefore of paramount importance that Judy is counselled carefully in order to discuss the risks of treatment and the optimisation of her health. Withdrawal of, or switch from valproate at this stage of pregnancy is associated with a significant risk of GTCSs with potential harm to the mother and foetus, with uncertain neurodevelopmental effects. This is an unfortunate situation that hopefully can be avoided with pregnancy planning, proactive pre-pregnancy counselling, consideration of AED changes prior to pregnancy, and use of valproate in women with childbearing potential only when absolutely necessary. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

ILAE statement: This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent official policy or the position of the ILAE.

This work has been partly funded by NordForsk Project #83796 (TT). TT has received speaker's honoraria to his institution from Eisai, Sanofi, Sun Pharma, UCB, and Sandoz, and research support from Stockholm County Council, EU, CURE, GSK, UCB, Eisai, and Bial. DB and SK report no disclosures. KM is funded by NIH NINDS, NICHD #2U01-NS038455 and has also received research support from Sunovion Pharmaceuticals, and travel support from UCB Pharma. The Epilepsy Study Consortium pays Dr. Meador's university for his research consultant time related to Eisai, GW Pharmaceuticals, NeuroPace, Novartis, Supernus, Upsher-Smith Laboratories, UCB Pharma, and Vivus Pharmaceuticals. PBP is funded by NIH NINDS, NICHD #2U01-NS038455 and has also received research support from Epilepsy Foundation, and honoraria and travel support from the American Epilepsy Society, American Academy of Neurology, Epilepsy Foundation, National Institutes of Health, and academic institutions for CME lectures. The authors thank P. Emma Voinescu, MD, PhD, for her contribution to the management table. RB is funded by a National Institute for Health Research grant (PDF-2013-06-041). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. RB has received a consultancy fee from UCB Pharma on one occasion, for a matter unrelated to this subject area.

References

Abe K, Hamada H, Yamada T, Obata-Yasuoka M, Minakami H, Yoshikawa H. Impact of planning of pregnancy in women with epilepsy on seizure control during pregnancy and on maternal and neonatal outcomes. *Seizure* 2014; 23(2): 112-6.

Adab N, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2001; 70(1): 15-21.

Adab N, Kini U, Vinten J, *et al.* The longer term outcome of children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2004; 75(11): 1575-83.

Almgren M, Kallen B, Lavebratt C. Population-based study of antiepileptic drug exposure in utero-influence on head circumference in newborns. *Seizure* 2009; 18(10): 672-5.

Baker GA, Bromley RL, Briggs M, *et al*. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. *Neurology* 2015; 84(4): 382-90.

Battino D, Kaneko S, Andermann E, *et al*. Intrauterine growth in the offspring of epileptic women: a prospective multicenter study. *Epilepsy Res* 1999; 36(1): 53-60.

Battino D, Tomson T, Bonizzoni E, *et al*. Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry. *Epilepsia* 2013; 54(9): 1621-7.

Bech LF, Polcwiartek C, Kragholm K, *et al*. In utero exposure to antiepileptic drugs is associated with learning disabilities among offspring. *J Neurol Neurosurg Psychiatry* 2018; 89(12): 1324-31.

Betts T, Fox C. Proactive pre-conception counselling for women with epilepsy-is it effective? *Seizure* 1999; 8(6): 322-7.

Bjork M, Riedel B, Spigset O, *et al*. Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero. *JAMA Neurol* 2018; 75(2): 160-8.

Blotière PO, Raguideau F, Weill A, *et al*. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. *Neurology* 2019; 93(2): e167-80.

Blümcke I, Arzimanoglou A, Beniczky S, Wiebe S. Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy. *Epileptic Disord* 2019; 21(2): 129-40.

Borthen I, Eide MG, Daltveit AK, Gilhus NE. Obstetric outcome in women with epilepsy: a hospital-based, retrospective study. *BJOG* 2011; 118(8): 956-65.

Bromley RL, Mawer G, Love J, *et al*. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010; 51(10): 2058-65.

Bromley RL, Mawer GE, Briggs M, *et al*. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. *J Neurol Neurosurg Psychiatry* 2013; 84(6): 637-43.

Bromley RL, Weston J, Adab N, *et al*. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database Syst Rev* 2014; 10: CD010236.

Bromley RL, Calderbank R, Cheyne CP, *et al*. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. *Neurology* 2016; 87(18): 1943-53.

Bromley RL, Baker GA, Clayton-Smith J, Wood AG. Intellectual functioning in clinically confirmed fetal valproate syndrome. *Neurotoxicol Teratol* 2019; 71: 16-21.

Cagnetti C, Lattanzi S, Foschi N, Provinciali L, Silvestrini M. Seizure course during pregnancy in catamenial epilepsy. *Neurology* 2014; 83(4): 339-44.

Campbell E, Devenney E, Morrow J, *et al*. Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero. *Epilepsia* 2013; 54(1): 165-71.

Campbell E, Kennedy F, Russell A, *et al*. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry* 2014; 85(9): 1029-34.

Centers for Disease Control. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Recomm Rep* 1992; 41(RR-14): 1-7.

Chatzi L, Papadopoulou E, Koutra K, *et al*. Effect of high doses of folic acid supplementation in early pregnancy on child neurodevelopment at 18 months of age: the mother-child cohort 'Rhea' study in Crete, Greece. *Public Health Nutr* 2012; 15(9): 1728-36.

Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. *Arch Neurol* 2009; 66(8): 979-84.

Christensen J, Gronborg TK, Sorensen MJ, *et al*. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013; 309(16): 1696-703.

Christensen J, Pedersen LH, Sun Y, Dreier JW, Brikell I, Dalsgaard S. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring. *JAMA Netw Open* 2019; 2(1): e186606.

Cohen MJ, Meador KJ, Browning N, *et al*. Fetal antiepileptic drug exposure: motor, adaptive, and emotional/behavioral functioning at age 3 years. *Epilepsy Behav* 2011; 22(2): 240-6.

Cohen MJ, Meador KJ, May R, *et al*. Fetal antiepileptic drug exposure and learning and memory functioning at 6years of age: the NEAD prospective observational study. *Epilepsy Behav* 2019; 92: 154-64.

Crawford P, Hudson S. Understanding the information needs of women with epilepsy at different lifestages: results of the 'Ideal World' survey. *Seizure* 2003; 12(7): 502-7.

Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011; 96(7): 643-7.

Czeizel AE, Dudas I, Vereczkey A, Banhidy F. Folate deficiency and folic acid supplementation: the prevention of neural-tube defects and congenital heart defects. *Nutrients* 2013; 5(11): 4760-75.

De Jong J, Garne E, De Jong-Van Den Berg LT, Wang H. The risk of specific congenital anomalies in relation to newer antiepileptic drugs: a literature review. *Drugs Real World Outcomes* 2016; 3(2): 131-43.

Donaldson, Donaldson JO. Neurological disorders. In: Swiet MD. *Medical disorders in obstetric practice*. 4th Ed. London: Blackwell Science Ltd., 2002: 486-9.

Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. *Epilepsia* 2014; 55(7): e72-4.

Elkjaer LS, Bech BH, Sun Y, Laursen TM, Christensen J. Association between prenatal valproate exposure and performance on standardized language and mathematics tests in school-aged children. *JAMA Neurol* 2018; 75(6): 663-71.

European Medicines Agency. *Assessment report. Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data*. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_and_related_substances_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500177352.pdf. Accessed April 10, 2018.

FDA. *Drug Safety Communication: Valproate anti-seizure products contraindicated for migraine prevention in pregnant women due to decreased IQ scores in exposed children*. (Issued June 5, 2013). Available at: https://www.fda.gov/Drugs/DrugSafety/ucm350684.htm. Accessed September 12, 2017.

Fisher RS, Cross JH, French JA, *et al*. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58(4): 522-30.

Forsberg L, Wide K, Kallen B. School performance at age 16 in children exposed to antiepileptic drugs in utero-a population-based study. *Epilepsia* 2011; 52(2): 364-9.

Frankenburg FR. Folate supplementation: is it safe and effective? *J Clin Psychiatry* 2009; 70(5): 767.

Gaily E, Kantola-Sorsa E, Granström ML. Intelligence of children of epileptic mothers. *J Pediatr* 1988; 113(4): 677-84.

Gaily EK, Granström ML, Hiilesmaa VK, Bardy AH. Head circumference in children of epileptic mothers: contributions of drug exposure and genetic background. *Epilepsy Res* 1990; 5(3): 217-22.

Gaily E, Kantola-Sorsa E, Hiilesmaa V, *et al*. Normal intelligence in children with prenatal exposure to carbamazepine. *Neurology* 2004; 62(1): 28-32.

Galanti M, Newport DJ, Pennell PB, *et al*. Postpartum depression in women with epilepsy: influence of antiepileptic drugs in a prospective study. *Epilepsy Behav* 2009; 16(3): 426-30.

Harden CL, Pennell PB, Koppel BS, *et al*. Practice parameter update: management issues for women with epilepsy-focus on pregnancy (an evidence-based review): vitamin k, folic acid, blood levels, and breastfeeding. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology* 2009a; 73(2): 142-9.

Harden CL, Meador KJ, Pennell PB, *et al*. Management issues for women with epilepsy-focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009b; 50(5): 1237-46.

Hernandez-Diaz S, Smith CR, Shen A, *et al*. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012; 78(21): 1692-9.

Hernandez-Diaz S, Mcelrath TF, Pennell PB, Hauser WA, Yerby M, Holmes LB. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. *Ann Neurol* 2017; 82(3): 457-65.

Hernandez-Diaz S, Huybrechts KF, Desai RJ, *et al*. Topiramate use early in pregnancy and the risk of oral clefts: a pregnancy cohort study. *Neurology* 2018; 90(4): e342-51.

Herzog AG, Mandle HB, Cahill KE, Fowler KM, Hauser WA. Predictors of unintended pregnancy in women with epilepsy. *Neurology* 2017; 88(8): 728-33.

Hiilesmaa V, Teramo K. Fetal and maternal risks with seizures. In: Harden C, Thomas SV, Tomson T, Hoboken NJ. *Epilepsy in women*. Wiley-Blackwell, 2013: 115-27.

Hiilesmaa VK, Teramo K, Granström ML, Bardy AH. Fetal head growth retardation associated with maternal antiepileptic drugs. *Lancet* 1981; 2(8239): 165-7.

Holmes LB, Mittendorf R, Shen A, Smith CR, Hernandez-Diaz S. Fetal effects of anticonvulsant polytherapies: different risks from different drug combinations. *Arch Neurol* 2011; 68(10): 1275-81.

Huber-Mollema Y, Oort FJ, Lindhout D, Rodenburg R. Behavioral problems in children of mothers with epilepsy prenatally exposed to valproate, carbamazepine, lamotrigine, or levetiracetam monotherapy. *Epilepsia* 2019; 60(6): 1069-82.

Hunt S, Russell A, Smithson WH, *et al*. Topiramate in pregnancy: preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2008; 71(4): 272-6.

Husebye ESN, Gilhus NE, Riedel B, Spigset O, Daltveit AK, Bjork MH. Verbal abilities in children of mothers with epilepsy: association to maternal folate status. *Neurology* 2018; 91(9): e811-21.

Hvas CL, Henriksen TB, Ostergaard JR, Dam M. Epilepsy and pregnancy: effect of antiepileptic drugs and lifestyle on birthweight. *BJOG* 2000; 107(7): 896-902.

Ip S, Chung M, Raman G, Trikalinos TA, Lau J. A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries. *Breastfeed Med* 2009; 4(1): S17-30.

Johannessen Landmark C, Burns ML, Baftiu A, *et al*. Pharmacokinetic variability of valproate in women of childbearing age. *Epilepsia* 2017; 58(10): e142-6.

Johnson EL, Stowe ZN, Ritchie JC, *et al*. Carbamazepine clearance and seizure stability during pregnancy. *Epilepsy Behav* 2014; 33: 49-53.

Julvez J, Fortuny J, Mendez M, Torrent M, Ribas-Fito N, Sunyer J. Maternal use of folic acid supplements during pregnancy and four-year-old neurodevelopment in a population-based birth cohort. *Paediatr Perinat Epidemiol* 2009; 23(3): 199-206.

Karanam A, Pennell PB, French JA, *et al*. Lamotrigine clearance increases by 5 weeks gestational age: relationship to estradiol concentrations and gestational age. *Ann Neurol* 2018; 84(4): 556-63.

Keni RR, Jose M, Sarma PS, Thomas SV, & Kerala Registry of Epilepsy, Pregnancy Study Group. Teratogenicity of antiepileptic dual therapy: dose-dependent, drug-specific, or both? *Neurology* 2018; 90(9): e790-6.

Kilic D, Pedersen H, Kjaersgaard MI, *et al*. Birth outcomes after prenatal exposure to antiepileptic drugs-a population-based study. *Epilepsia* 2014; 55(11): 1714-21.

Kinney MO, Morrow J. Epilepsy in pregnancy. *BMJ* 2016; 353: i2880.

Kinney MO, Morrow J, Patterson CC, *et al*. Changing antiepilepsy drug-prescribing trends in women with epilepsy in the UK and Ireland and the impact on major congenital malformations. *J Neurol Neurosurg Psychiatry* 2018; 89(12): 1320-3.

Lopez-Fraile IP, Cid AO, Juste AO, Modrego PJ. Levetiracetam plasma level monitoring during pregnancy, delivery, and postpartum: clinical and outcome implications. *Epilepsy Behav* 2009; 15(3): 372-5.

Macdonald SC, Bateman BT, Mcelrath TF, Hernandez-Diaz S. Mortality and morbidity during delivery hospitalization among pregnant women with epilepsy in the United States. *JAMA Neurol* 2015; 72(9): 981-8.

Margulis AV, Hernandez-Diaz S, McElrath T, *et al*. Relation of in-utero exposure to antiepileptic drugs to pregnancy duration and size at birth. *PLoS One* 2019; 14(8): e0214180.

Mawhinney E, Campbell J, Craig J, *et al*. Valproate and the risk for congenital malformations: is formulation and dosage regime important? *Seizure* 2012; 21(3): 215-8.

Mawhinney E, Craig J, Morrow J, *et al*. Levetiracetam in pregnancy: results from the UK and Ireland epilepsy and pregnancy registers. *Neurology* 2013; 80(4): 400-5.

Mcgrath A, Sharpe L, Lah S, Parratt K. Pregnancy-related knowledge and information needs of women with epilepsy: a systematic review. *Epilepsy Behav* 2014; 31: 246-55.

Meadow SR. Anticonvulsant drugs and congenital abnormalities. *Lancet* 1968; 2(7581): 1296.

Meador KJ, Baker GA, Browning N, *et al*. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009; 360(16): 1597-605.

Meador KJ, Baker GA, Browning N, *et al*. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology* 2010; 75(22): 1954-60.

Meador KJ, Baker GA, Browning N, *et al*. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain* 2011; 134(2): 396-404.

Meador KJ, Baker GA, Browning N, *et al*. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013; 12(3): 244-52.

Meador KJ, Baker GA, Browning N, *et al*. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. *JAMA Pediatr* 2014; 168(8): 729-36.

Meador KJ, Pennell PB, May RC, *et al*. Changes in antiepileptic drug-prescribing patterns in pregnant women with epilepsy. *Epilepsy Behav* 2018; 84: 10-4.

Moore SJ, Turnpenny P, Quinn A, *et al*. A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet* 2000; 37(7): 489-97.

Morris MS, Jacques PF, Rosenberg IH, Selhub J. Circulating unmetabolized folic acid and 5-methyltetrahydrofolate in relation to anemia, macrocytosis, and cognitive test performance in American seniors. *Am J Clin Nutr* 2010; 91(6): 1733-44.

Morrow J, Russell A, Guthrie E, *et al*. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006; 77(2): 193-8.

Morrow JI, Hunt SJ, Russell AJ, *et al*. Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2009; 80(5): 506-11.

MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991; 338(8760): 131-7.

Murray LK, Smith MJ, Jadavji NM. Maternal oversupplementation with folic acid and its impact on neurodevelopment of offspring. *Nutr Rev* 2018; 76(9): 708-21.

Nadebaum C, Anderson V, Vajda F, Reutens D, Barton S, Wood A. The Australian brain and cognition and antiepileptic drugs study: IQ in school-aged children exposed to sodium valproate and polytherapy. *J Int Neuropsychol Soc* 2011; 17(1): 133-42.

Nei M, Daly S, Liporace J. A maternal complex partial seizure in labor can affect fetal heart rate. *Neurology* 1998; 51(3): 904-6.

NICE. *Epilepsies: Diagnosis And Management*. 2012.

Pennell PB. Pregnancy, epilepsy, and women's issues. *Continuum* (Minneap Minn) 2013; 19(3 Epilepsy): 697-714.

Pennell and McElrath, Pennell PB, McElrath T. Risks associated with epilepsy during pregnancy and postpartum period. In: Dashe JF. *UpToDate*. UpToDate Inc: Waltham, MA. (Accessed on March 13, 2019).

Pennell PB, Peng L, Newport DJ, *et al*. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology* 2008; 70(22): 2130-6.

Pennell PB, Klein AM, Browning N, *et al*. Differential effects of antiepileptic drugs on neonatal outcomes. *Epilepsy Behav* 2012; 24(4): 449-56.

Polepally AR, Pennell PB, Brundage RC, *et al*. Model-based lamotrigine clearance changes during pregnancy: clinical implication. *Ann Clin Transl Neurol* 2014; 1(2): 99-106.

Rasalam AD, Hailey H, Williams JH, *et al*. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev Med Child Neurol* 2005; 47(8): 551-5.

Reisinger TL, Newman M, Loring DW, Pennell PB, Meador KJ. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. *Epilepsy Behav* 2013; 29(1): 13-8.

Rihtman T, Parush S, Ornoy A. Preliminary findings of the developmental effects of in utero exposure to topiramate. *Reprod Toxicol* 2012; 34(3): 308-11.

Rihtman T, Parush S, Ornoy A. Developmental outcomes at preschool age after fetal exposure to valproic acid and lamotrigine: cognitive, motor, sensory and behavioral function. *Reprod Toxicol* 2013; 41: 115-25.

Roth C, Magnus P, Schjolberg S, *et al*. Folic acid supplements in pregnancy and severe language delay in children. *JAMA* 2011; 306(14): 1566-73.

Rovet J, Cole S, Nulman I, Scolnik D, Altmann D, Koren G. Effects of maternal epilepsy on children's neurodevelopment. *Child Neuropsychology* 1995; 1(2): 150-7.

Roza SJ, Van Batenburg-Eddes T, Steegers EA, *et al*. Maternal folic acid supplement use in early pregnancy and child behavioural problems: The Generation R Study. *Br J Nutr* 2010; 103(3): 445-52.

Rozendaal AM, van Essen AJ, te Meerman GJ, *et al*. Periconceptional folic acid associated with an increased risk of oral clefts relative to non-folate related malformations in the Northern Netherlands: a population based case-control study. *Eur J Epidemiol* 2013; 28(11): 875-87.

Sahoo S, Klein P. Maternal complex partial seizure associated with fetal distress. *Arch Neurol* 2005; 62(8): 1304-5.

Schlotz W, Jones A, Phillips DI, Gale CR, Robinson SM, Godfrey KM. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. *J Child Psychol Psychiatry* 2010; 51(5): 594-602.

Scolnik D, Nulman I, Rovet J, *et al*. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. *JAMA* 1994; 271(10): 767-70.

Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 2011; 76(4): 383-9.

Shallcross R, Bromley RL, Cheyne CP, *et al*. In utero exposure to levetiracetam vs valproate: development and language at 3 years of age. *Neurology* 2014; 82(3): 213-21.

Skorka A, Gieruszczak-Bialek D, Piescik M, Szajewska H. Effects of prenatal and/or postnatal (maternal and/or child) folic acid supplementation on the mental performance of children. *Crit Rev Food Sci Nutr* 2012; 52(11): 959-64.

Sveberg L, Svalheim S, Tauboll E. The impact of seizures on pregnancy and delivery. *Seizure* 2015; 28: 35-8.

Thomas SV, Ajaykumar B, Sindhu K, Nair MK, George B, Sarma PS. Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy Behav* 2008; 13(1): 229-36.

Thomas SV, Syam U, Devi JS. Predictors of seizures during pregnancy in women with epilepsy. *Epilepsia* 2012; 53(5): e85-8.

Tomson T, Palm R, Kallen K, *et al*. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007; 48(6): 1111-6.

Tomson T, Battino D, Craig J, *et al*. Pregnancy registries: differences, similarities, and possible harmonization. *Epilepsia* 2010; 51(5): 909-15.

Tomson T, Johannessen Landmark C, Battino D. Antiepileptic drug treatment in pregnancy: changes in drug disposition and their clinical implications. *Epilepsia* 2013; 54(3): 405-14.

Tomson T, Battino D, Bonizzoni E, *et al*. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. *Neurology* 2015; 85(10): 866-72.

Tomson T, Battino D, Perucca E. Valproic acid after five decades of use in epilepsy: time to reconsider the indications of a time-honoured drug. *Lancet Neurol* 2016; 15(2): 210-8.

Tomson T, Battino D, Bonizzoni E, *et al*. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Lancet Neurol* 2018; 17(6): 530-8.

Tomson T, Battino D, Bonizzoni E, *et al*. Declining malformation rates with changed antiepileptic drug prescribing: an observational study. *Neurology* 2019; 93(9): e831-40.

Turner K, Piazzini A, Franza A, *et al*. Postpartum depression in women with epilepsy versus women without epilepsy. *Epilepsy Behav* 2006; 9(2): 293-7.

Vajda FJ, Hitchcock A, Graham J, O'brien T, Lander C, Eadie M. Seizure control in antiepileptic drug-treated pregnancy. *Epilepsia* 2008; 49(1): 172-6.

Vajda FJ, O'brien TJ, Lander CM, Graham J, Roten A, Eadie MJ. Teratogenesis in repeated pregnancies in antiepileptic drug-treated women. *Epilepsia* 2013; 54(1): 181-6.

Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. *Epilepsia* 2009; 50(9): 2130-9.

Veiby G, Daltveit AK, Schjolberg S, *et al*. Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia* 2013a; 54(8): 1462-72.

Veiby G, Engelsen BA, Gilhus NE. Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort study on children of women with epilepsy. *JAMA Neurol* 2013b; 70(11): 1367-74.

Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. *J Neurol* 2014; 261(3): 579-88.

Veroniki AA, Cogo E, Rios P, *et al*. Comparative safety of antiepileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. *BMC Med* 2017; 15(1): 95.

Villamor E, Rifas-Shiman SL, Gillman MW, Oken E. Maternal intake of methyl-donor nutrients and child cognition at 3 years of age. *Paediatr Perinat Epidemiol* 2012; 26(4): 328-35.

Voinescu PE, Pennell PB. Delivery of a personalized treatment approach to women with epilepsy. *Semin Neurol* 2017; 37(6): 611-23.

Voinescu PE, Park S, Chen LQ, *et al*. Antiepileptic drug clearances during pregnancy and clinical implications for women with epilepsy. *Neurology* 2018; 91(13): e1228-36.

Wehby GL, Murray JC. The effects of prenatal use of folic acid and other dietary supplements on early child development. *Matern Child Health J* 2008; 12(2): 180-7.

Westin AA, Reimers A, Helde G, Nakken KO, Brodtkorb E. Serum concentration/dose ratio of levetiracetam before, during and after pregnancy. *Seizure* 2008; 17(2): 192-8.

Weston J, Bromley R, Jackson CF, *et al*. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev* 2016; 11: CD010224.

Wide K, Winbladh B, Tomson T, Kallen B. Body dimensions of infants exposed to antiepileptic drugs in utero: observations spanning 25 years. *Epilepsia* 2000a; 41(7): 854-61.

Wide K, Winbladh B, Tomson T, Sars-Zimmer K, Berggren E. Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study. *Dev Med Child Neurol* 2000b; 42(2): 87-92.

Wide K, Henning E, Tomson T, Winbladh B. Psychomotor development in preschool children exposed to antiepileptic drugs in utero. *Acta Paediatr* 2002; 91(4): 409-14.

Wilson RD, Genetics C, Motherisk C. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. *J Obstet Gynaecol Can* 2007; 29(12): 1003-13.

Yerby MS, Friel PN, Mccormick K, *et al*. Pharmacokinetics of anticonvulsants in pregnancy: alterations in plasma protein binding. *Epilepsy Res* 1990; 5(3): 223-8.

Yerby MS, Friel PN, Mccormick K. Antiepileptic drug disposition during pregnancy. *Neurology* 1992; 42(4): 12-6.

TEST YOURSELF

(1) What is the risk of major congenital malformations in offspring after maternal use of valproate?

(2) Why is it important for women with epilepsy taking AEDs to also take periconceptional folate?

(3) Serum concentrations of many antiepileptic drugs tend to decrease during pregnancy. What level of decrease is associated with a significant risk of deterioration in seizure control?

(4) Provide the 2 most frequent causes of breakthrough seizures during pregnancy.

(5) Which of the statements below are not true:

A. During the newborn period bathing of the baby with the mother alone should be avoided.
B. During the newborn period the mother should priviliege using a baby carrier when walking around with the baby;
C. Breastfeeding should be prohibited
D. In the early postpartum period, the mother should also be discouraged from taking a bath by herself behind a closed, locked door or when no other adult is around.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".