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Management of epilepsy during pregnancy

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Abstract

Over a million women with epilepsy are of childbearing age in the USA and require careful consideration of not only type of antiepileptic drug (AED) but also dosage, in the event of a planned or unplanned pregnancy. Careful selection of AEDs can lower the potential adverse effects of AEDs while maintaining seizure control for the health of not only on the patient, the mother, but also the unborn fetus. The number of treatment options has increased significantly in the last 20 years and remarkable progress has been made in characterizing the risks AEDs pose to pregnant women and fetuses. There are now robust data on teratogenesis, a growing body of data on neonatal/obstetrical outcomes and on neurodevelopmental problems associated with each AED, and some data about seizure control during pregnancy. Based on clinical evidence so far, levetiracetam and lamotrigine have emerged as the safest during pregnancy, although others may also be suitable. Despite being a common belief, not all polytherapy combinations may be detrimental, especially when avoiding valproate and topiramate. Here, we review the available clinical research, highlighting recent findings and provide thoughts for future directions in the field.

Keywords

epilepsy; pregnancy; major congenital malformations; neonatal complications; neurodevelopmental outcome; antiepileptic drugs

Epilepsy is one of the most common neurological disorders that requires continuous treatment during pregnancy, though unfortunately with known teratogens. Pregnancy is a special state in which physiological changes can alter the natural course of diseases and change the pharmacokinetics of medications, making the therapeutic management more complicated. In addition, pregnancy poses a special therapeutic challenge during which the adverse effects of the antiepileptic drug (AED) have to be weighed against the adverse

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effects of untreated or undertreated disease not only on the woman, but also on her developing fetus. These adverse effects can impact both the mother and the fetus during the pregnancy, but also during delivery and the perinatal period, and they can have a long-term developmental impact on the child.

A noteworthy fact is that AEDs have increased in number significantly over the last 20 years and their use extends beyond epilepsy to include psychiatric diseases, migraines and other pain syndromes. The prevalence of AED prescriptions for women 15–44 years old in the USA increased significantly in the last decades [1], with over 4 million annual prescriptions written for epilepsy (20.7%), mental illnesses (47.9%) and pain disorders (22.2%) [1]. Yet, many of the AEDs still have an insufficiently characterized safety profile for pregnant women and their offspring.

Most data informing our understanding of epilepsy and epilepsy therapy during pregnancy come from five types of sources: national pregnancy registries: Sweden, Norway, Finland and Denmark; epilepsy-specific registries: USA/Canada – North American AED Pregnancy Registry (NAAPR), the International Registry of Antiepileptic Drugs and Pregnancy (EURAP, consisting of more than 40 countries worldwide), including UK/Ireland Epilepsy and Pregnancy Register, Australian Pregnancy Register of AEDs and Indian Registry of Epilepsy and Pregnancy (Kerala); drug-specific registries for levetiracetam (LEV) and lamotrigine (LTG), set up by pharmaceutical companies; the European Surveillance of Congenital Anomalies (EUROCAT) database (including 14 European countries) and the US National Birth Defects Prevention Study (NBDPS) and longitudinal studies, for example, the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, an instrumental prospective observational study of pregnant women on AED monotherapy and their children.

This review aims to summarize the relevant literature on pregnancy-related issues that need to be considered when choosing a therapeutic approach for women with epilepsy (WWE) (Figure 1), with a focus on work published in the past 5 years. Note though that while we try to unite their findings, the studies included have different designs and, especially, their definition of exposure is different. NAAPR and EURAP study included women on the same AED monotherapy during the first trimester. Note that EURAP further stratify their conclusions based specifically on the dose used at the time of conception only, and not the entire pregnancy or even the first trimester [2]. National medical birth registries, on the other hand, define exposure as any length of monotherapy starting 30 days prior to conception up to the delivery date. In addition, the data may vary based on the interval allowed for reporting major congenital malformations (MCMs): for example, NAAPR used data on reported MCMs within the first 12 weeks of life [3], while EURAP's end point was 12 months [2]. Additionally, all of these registries vary in what they include as a MCM, which confounds the interpretation further. Another limitation to consider when interpreting data from these various registries is that comparisons to a true control population is often not possible, and comparisons are usually only possible between different AED exposures, or more rarely, with no AED exposure in newborns of women with epilepsy.

The impact of pregnancy on epilepsy

Research to date has revealed no overall seizure frequency variation during pregnancy, although a significant fraction of women may experience some variability during pregnancy. The majority of studies, in their analysis, did not differentiate between WWE on treatment or not on treatment and did not include an appropriate non-pregnant WWE control group to distinguish between pregnancy-related changes versus the natural course of seizure frequency for WWE. Review of relevant literature up to 2007 revealed large variations in the percentage of patients with unchanged seizure frequency ranging from 54 to 80%; the percent of women with a decrease in seizure frequency ranged from 3 to 24% and the percentage of women with an increase in seizure frequency ranged from 14 to 32% [4]. A recent analysis of 3806 pregnancies in the 2013 EURAP study revealed that 66.6% of WWE remained seizure-free throughout pregnancy, while worsening in seizure control occurred in 15.8% of pregnancies, although comparison was seizure control during the second and third trimesters compared with the first trimester [5]. A more recent small prospective case–control study, with matched non-pregnant WWE controls, confirmed prior observations and showed that during pregnancy 72% of cases remained ‘unchanged’ (with ~80% of these seizure free) while 8 and 19% respectively, ‘improved’ and ‘worsened’, numbers not significantly different from the non-pregnant controls [6].

A useful observation is that the seizure freedom rate seems to be higher in women with genetic (idiopathic) generalized epilepsies (73.6%) than in those with focal epilepsy syndromes (59.5%) [5]. Women with focal-onset seizures had higher risk for seizures during pregnancy with two peaks of seizure relapse, one around the second to third month and another one around the sixth month. However, seizure relapse overall was highest during the three peripartum days. A good predictor for seizure relapse during pregnancy was the pre-pregnancy seizure frequency. The probable rate of remaining seizure-free during pregnancy for WWE who are seizure-free for at least 9 months to 1 year prior to pregnancy is estimated to be 84–92% [4], while women who had seizures in the prepregnancy month had 15-times higher risk for seizures during pregnancy [7]. A recent study of data gathered in the Australian Pregnancy Register since 1999 [8], included evaluation of 148 WWE on no AED and similarly concluded that the main determinant for the risk of seizure occurrence in AED-untreated pregnancies seemed to be whether the woman’s epilepsy was ‘active’ or ‘inactive’ (presence of seizures) in the year prior to pregnancy with rates of any seizures 82.4 versus 29.7% (relative risk [RR]: 4.00; 95% CI: 2.39–6.70), and convulsive seizures 36.5 versus 12.2% (RR: 3.00; 95% CI: 1.52–5.93), respectively.

There are many changes during pregnancy that can alter seizure frequency: physiologic changes including hormonal variations, changes in drug absorption, distribution, metabolism and excretion (AED pharmacokinetics) [9,10], as well as psychosocial adjustments with new stresses and sleep deprivation that can lower seizure threshold. Another important factor is poor adherence with medications due to the perception that AEDs are harmful to the fetus. Unfortunately, WWE often lack adequate knowledge about epilepsy and preconception planning, pregnancy, and childbirth issues to make truly informed decisions about their treatment regimens [11].

The impact of epilepsy on pregnancy

There are little data on untreated epilepsy in pregnancy and fetal outcomes. Moreover, fetal risks associated with maternal seizures are not well investigated. The old concern that epilepsy *per se* may increase the risk for MCMs has been long dismissed [12]. MCMs are defined as structural abnormalities that interfere significantly with function, life and/or require surgery for correction. The rates in the general population are similar to that of WWE on no AEDs and vary between 1.6 and 3.2%, while the average rate for WWE on any AEDs is approximately two- to threefold higher varying between 3.1 and 9%. Other anomalies that do not interfere with function to require intervention are considered minor and they affect 6–20% of infants born to WWE, approximately 2.5-fold the rate of the general population [9].

A recent study on untreated epilepsy in pregnancy compared the seizure control and MCM rate for 148 WWE on no AED and 1532 WWE on treatment with an AED [8] and showed that, as expected, members of the untreated group were more likely to have epileptic seizures of any type during pregnancy compared with the treated group (56.1 vs 46.9%), as well as more convulsive seizures (24.3 vs 18.9%), leading to approximately half of the untreated patients to be started on treatment by term. Fetal MCM rates, however, were similar in the untreated and treated groups if pregnancies exposed to known high-risk AED teratogens (valproate [VPA] and topiramate [TPM]) were excluded. The study does not address, unfortunately, neonatal or obstetrical outcomes. It mentions neonatal death rates of 1.3% in the untreated group and 0.8% in the treated group, but the difference does not reach statistical significance.

A single brief tonic-clonic seizure has been shown to cause depression of the fetal heart rate for more than 20 min; longer or repetitive tonic-clonic seizures can trigger maternal and fetal hypoxia, acidosis and possible miscarriages and stillbirths [13]. In addition, many types of seizures can cause trauma with an added risk of infection, premature labor and abruptio placentae (occurring in 1–5% of minor and 20–50% of major blunt injuries) [9].

There are very little data published on obstetrical complications, but Harden *et al.* concluded in their review that the risk of premature contractions or premature labor and delivery for WWE taking AEDs is probably no greater than 1.5-times, while there is possibly a substantially increased risk of premature contractions and premature labor and delivery during pregnancy for WWE who smoke [4]. Studies about maternal mortality come from the UK: Adab *et al.* in 2004 estimated a 10-fold increase in mortality during pregnancy in WWE compared with women without epilepsy [14], and a more recent study based on a report from the United Kingdom Confidential Enquiries into Maternal Deaths confirmed previous estimates and calculated a rate of 1:1000 women with epilepsy dying during or shortly after pregnancy [15]. Sixty-four percent (9/14) of maternal deaths were in WWE on LTG. The authors speculate that this finding may reflect UK's prescribing practice of relatively low doses, but it can also be correlated with poor seizure control on LTG and the need to adjust levels during pregnancy, potentially neglected.

A previous retrospective study suggested that exposure to more than five generalized tonic-clonic convulsions (GTCC) seizures during pregnancy is associated with reduced cognitive ability [14]. A more recent study did not reveal any association between seizures and child's IQ, but convulsive seizures were associated with an increased need for additional educational support [16].

Data on individual AED impact on fetal development, neonatal outcomes, pharmacokinetics & efficacy in controlling seizures

There are several aspects to consider when choosing an AED for a woman of childbearing age: teratogenicity, neonatal outcomes (e.g., birth weight, head circumference, APGAR score, need for neonatal intensive care unit), obstetrical outcomes (e.g., preterm delivery and C-section rates) as well as long-term neurodevelopmental impact (IQ, verbal and non-verbal abilities, memory, behavior and any predisposition for autism spectrum disorders). Last, but not least, seizure control is essential and needs to be a priority given detrimental effects of uncontrolled seizures in pregnancy, as described above. There should be a proactive discussion and continuous education of WWE such that the best individual choice is made prior to pregnancy, keeping in mind that over half of the pregnancies in WWE in the USA are not planned and by the time WWE find out about their pregnancy, it is often too late to adjust the AED regimen to avoid malformations. Organogenesis occurs within the first 4–10 weeks of gestation (post-conception) and structural abnormalities established during this window will be irreversible. Importantly, the neural tube closure occurs between the third and the fourth week of gestation, around the time when pregnancy is confirmed, while the heart and face structures form within the first 5–10 weeks postconception, rendering CNS malformations harder to prevent compared with ventricular septal defects, cleft lip or cleft maxillary palate. Neonatal outcomes should not be neglected either when selecting an AED: small for gestational age (SGA) newborns have an increased risk for perinatal mortality and morbidity later in life, including impaired neurodevelopment, cardiovascular diseases and diabetes [17].

When assessing the risk for MCMs for a particular pregnancy, besides the AEDs used, an important factor to take into account is the individual genetic make-up: it was shown that a parental history of MCM increases the risk more than fourfold (odds ratio [OR]: 4.4; 95% CI: 2.06–9.23) [2,18] and a history of fetal malformations in a previous pregnancy on the same AED leads to more than 15-fold increased risk (OR: 17.6; 95% CI: 4.5–68.7) [19].

Prior to pregnancy, another critical aspect is the AED interaction with oral contraceptive pills as most of them are inducers of sex steroids metabolism and not suitable to be used with the lowest-dose oral contraceptive pills. Presented in a chronological order of FDA approval, Table 1 shows the list of currently available AEDs and their effect on sex steroid metabolism.

Learnings about AED monotherapy use in pregnancy over the past 20 years are described below and are summarized in Table 2. We aim to synthesize important information on teratogenicity, neonatal and obstetrical outcomes, neurodevelopmental outcomes and any association with autistic spectrum disorders, as well as pharmacokinetics during pregnancy

and attempts to characterize seizure control during pregnancy. While the pregnancy registries can offer robust data on teratogenicity, they gather less information about neonatal and obstetrical outcomes. To fully assess for the impact on neurodevelopmental outcomes, longitudinal studies are necessary, although there are no randomized controlled trials, some prospective cohort studies started to tackle this complex question [16,20–27]. Finally, seizure control is one of the hardest aspects to analyze given not only the lack of randomized studies, but also the variety of seizure types and epilepsy syndromes with variable severities, that in itself directly impacts AED choices. Given that these data are from pregnancy registries that do not have enough info about patients seizure types and frequency to adjust for all of the confounding variables, comparing individual AED efficacy based on the reported % of WWE that have seizures during pregnancy, without information about the pre-pregnancy seizure frequency, AED levels or dose adjustment during pregnancy, seems to be very limited, but no better information is yet available. A thorough retrospective study found that for all monotherapies, seizures worsened significantly when the AED blood concentrations fell to <65% of preconception baseline [28]. This may be one important explanation for apparent seizure worsening, especially in WWE on monotherapy on AEDs with altered pharmacokinetics during pregnancy.

Phenobarbital (PB) is one of the oldest first-generation AEDs, with significant side effects and rarely used as a first-line treatment in adults in the USA now, but still used extensively in other parts of the world, especially for generalized epilepsy, due to its low cost and effectiveness.

Both the NAAPR and EURAP studies show a high MCM rate of 6–7% that is dose-dependent, with doses >150 mg/day resulting in a significantly increased risk when compared with doses ≤150 mg (OR: 3.2; 95% CI: 1.11–9.45). However, when compared with LTG <300 mg/daily, even lower doses of PB <150 mg/day are associated with a significantly increased MCM risk of 2.5-fold (95% CI: 1.11–5.85) [2]. There are overwhelmingly more cardiac malformations and oral clefts than urogenital or neural tube defects (21 pooled studies by Tomson and Battino [29]).

There are little data on neonatal or neurodevelopmental outcomes, but a study from Denmark from 1995 [30] raised the concern that PB exposure during early development can have long-term deleterious effects on cognitive performance, especially on verbal intelligence scores leading to the recommendation that PB should be avoided during pregnancy, if possible, to reduce the risk of poor cognitive outcomes [12]. There is no autism spectrum disorder report for children with *in utero* PB exposure [31].

Phenobarbital is 50% bound to serum proteins and hepatically metabolized by CYP2C19 and 2E1. Its clearance has been reported to increase up to 60% in pregnancy leading to a decrease in free phenobarbital concentration by 50% [9]. Based on these findings, its level should be monitored and dose adjusted accordingly during pregnancy.

Data from NAAPR suggests that <20% of WWE on PB have seizures during pregnancy and EURAP gives numbers of ~30%, rendering PB an efficacious AED [3,5,32]. Given its

limited use currently, no recent studies are available to assess for its efficacy in comparison to newer AEDs.

Phenytoin (PHT) is a first-generation, broad-spectrum AED, but rarely the agent of choice in pregnant women. Data on its use in pregnancy are thus limited and most studies have a lower number of subjects for PHT compared with other AEDs.

Fetal hydantoin syndrome has been known for several decades based on observations made initially in animals and later in humans of hand/phalangeal anomalies and facial dysmorphism. Most of these are minor anomalies and pose no direct health problems, but raise the concern for intellectual disability. When compared with other first-generation AEDs, especially VPA, PHT has a favorable MCM profile. The NAAPR study reported a MCM rate of 2.9%, not significantly different than carbamazepine (CBZ) and with a RR of 1.5 (95% CI: 0.7–2.9) when compared with LTG [3]. Other registries have reported a MCM rate ranging from 2.4 to 7% [2,33]. Regarding particular MCMs, data so far seem to indicate a higher risk for cardiac malformation, urogenital malformations and oral clefts, but not neural tube defects [29].

Neonatal outcomes for PHT were favorable in the NEAD study cohort, with no increase in SGA birth weight and a microcephaly rate lower than that of other AEDs studied (8% at birth) that normalized by 2 years, a profile comparable to that of LTG [17].

The same NEAD study shows that the age-6 IQ was similar among children exposed to PHT, CBZ and LTG. Moreover, right-handedness rate was normal and there was no difference among verbal and non-verbal abilities. The general memory index may have been slightly worse than that for LTG and CBZ, although no direct comparison is provided, thus hard to know the significance [20]. A recent Cochrane review [31] finds again no significant difference in the developmental and intellectual quotient among the studies analyzed, but mentions older studies that raised concerns for specific cognitive dysfunctions, in particular poor language abilities, and delayed motor development [12]. There are no published studies to associate PHT exposure with autism spectrum disorder.

Pregnancy can affect the disposition of PHT significantly by a decrease in protein binding, given that about 90% is bound to plasma proteins in the non-pregnant state, as well as by induced metabolism by the CYP450 enzymes in the liver. Thus, total drug levels can fall by up to 60%, with free-PHT concentration declining to a lesser extent, by 16–40% in the third trimester [9,10]. PHT monitoring during pregnancy is necessary, with free concentrations more useful in directing dose adjustments.

In terms of efficacy, PHT seems to be similar to CBZ, modestly better when compared with LTG and LEV, as per NAAPR data (n = 416), with 25–30% WWE having at least one seizure during their pregnancy [3]. Data from the Australian Pregnancy Register, with a much smaller n (41), suggest worse seizure control with PHT monotherapy, with 31% pregnant WWE having at least one GTCC and 51% having any type of seizure, comparable to their pregnant women on LTG, and worse than seizure control in pregnant women on LEV [32].

Carbamazepine is a relatively older AED and a great choice for WWE of childbearing age given its low cost and wide availability internationally.

The rate for MCM in children born to women on CBZ enrolled in the NAAPR was found to be 3% (95% CI: 2.1–4.2), with a RR of 1.5 (95% CI: 0.9–2.5) when compared with LTG, and 2.7 (95% CI: 1–7%) when compared with the unexposed group [3]. Based on the dose used at the time of conception, EURAP study differentiated further the risk of low-dose versus medium- and high-dose CBZ and showed a dose-dependent increase in the rates of MCM reported by 1 year of 3.4% with CBZ dose <400 mg/day, 5.3% with CBZ 400–1000 mg/day, 8.7% if CBZ dose >1000 mg/day leading to a RR when compared with LTG <300 mg/day exposed group of 1.6 (95% CI: 0.56–4.53), 2.5 (95% CI: 1.45–4.48) and 4.6, respectively, the last two being statistically different [2]. While the MCM rate seen with exposure to over 1000 mg daily in the more recent study using the UK/Ireland Epilepsy and Pregnancy Register was lower (MCM rate 5.2%), the OR observed for malformations associated with exposure to CBZ doses of >1000 versus <500 mg was 2.82 (95% CI: 1.20–6.64), very similar to that originally reported OR for the highest versus lowest dose in the EURAP 2011 study of 2.9 (95% CI: 1.04–8.00) [34]. More recently, Veiby *et al.* reported a similar MCM rate for CBZ of 2.9% overall, but a lower RR of 1.06 (with a tight 95% CI 0.68–1.66), undistinguishable from unexposed healthy reference group, based on Norway Medical Birth Registry data [35].

Evaluation of neonatal outcomes in the NEAD cohort demonstrated a slight increased risk for SGA birth weight (12.9), but the weight corrected by 3 years of age [17]. Similarly, CBZ was also associated with higher rates of microcephaly at birth (19%) and 12 months of age (24%), but the microcephaly rate almost normalized to 4% by 36 months. The study was not powered to segregate the group of CBZ-exposed children based on the dose. Another study found that offspring of WWE on CBZ monotherapy therapy had a 1.92 (95% CI: 1.02–3.60) increased risk of perinatal mortality, a mild increase in preterm birth rate and low birth weight, although no increase in SGA rate. Full-term offspring had a more than twofold increased risk of needing respiratory treatment compared with non-exposed offspring [36].

The neurodevelopmental profile for CBZ is favorable across several studies [12]. Reports from the NEAD study indicated a possible dose-dependent impairment in verbal abilities at 3 years of age, but the investigators were unable to replicate this finding with testing at 6 years of age [20,21]. Thorough meta-analyses in a recent Cochrane review also revealed no significant difference in the developmental and intelligence quotients for CBZ-exposed children when compared with unexposed or LTG-exposed children [31]. Also, several studies investigated the relationship between dose of CBZ and child cognitive outcome and all failed to demonstrate a significant association between increasing doses and reduced child global cognitive ability [23]. There is only one recently published study from the UK showing an increased frequency of IQ <85 and poorer verbal abilities [16]. No significant increase in autism spectrum disorder was found for children exposed *in utero* to CBZ in two studies [23,24].

CBZ is 70–80% protein-bound and is metabolized by the hepatic cytochrome P450 3A4 isoenzyme to CBZ 10,11-epoxide (CBZ-EPO), an active anticonvulsant with potential for

structural and neurodevelopmental teratogenic effects. The most recent results on CBZ variations during pregnancy come from a small prospective cohort study that carefully analyzed CBZ, free CBZ, CBZ-EPO and free CBZ-EPO clearance and seizure frequency [37]. It showed a significant increase in the free CBZ fraction, from 0.23 at baseline to a maximum of 0.32 in the third trimester ($p = 0.008$), but no significant change in the clearance of total CBZ or free or total CBZ-EPO throughout pregnancy and no correlation with seizure frequency. Thus, there is yet another element in favor of CBZ: it does not need drug level monitoring and dose adjustment may not be necessary during or after pregnancy.

With an indication for focal onset seizures, CBZ seems to provide good seizure control with 67.3% pregnant WWE on CBZ free from seizures according to the most recent data from EURAP [5]. The authors noted that a lower percentage of pregnant women experienced total seizure control with the highest dose of CBZ (41.9%), an apparent paradox that likely reflects harder to control epilepsy in women who received higher AED doses. The same study reports one of the highest risks for seizures during delivery for WWE on CBZ, similar to that of WWE on LTG (2.6%). The recent Australian Pregnancy Register report reveals a slightly higher percentage of WWE on CBZ monotherapy experiencing any type of seizures (37.8%) and GTCC (18.5%) during pregnancy [32]. Note though, that regardless of AED used, seizure relapse during pregnancy seems to be more frequent with focal epilepsy syndromes [5], the main indication for CBZ therapy.

Valproic acid is a broad-spectrum AED, frequently prescribed for epilepsy as well as for bipolar disorder and migraine headache. Various research studies across different parts of the world have consistently provided data confirming an association with an increased rate of MCM and worse developmental outcomes when compared with other AEDs. Given that VPA is an efficacious treatment and one of the most effective for generalized and unclassified or mixed seizure types [38], it is still some-times prescribed for women with epilepsy of childbearing age. Recommendations are that it is prescribed only after other AED trials have failed for epilepsy and bipolar disorder, and it is now Category X for treatment of migraine headaches during pregnancy [39,40].

The rates of MCMs for VPA-exposed pregnancies are the highest among all AEDs for all studies. MCM rates were 9–10% in both NAAPR and EURAP studies and, compared with LTG, the RR was 5.1 (95% CI: 3.0–8.5) [2,3]. There is a dose-dependent risk reported initially by EURAP, with MCM rates of 5.6% for VPA <700 mg, 10.4% for VPA 700–1500 mg and 24.2% for VPA >1500 mg; and slightly lower rates reported recently from the UK/Ireland registries as 5.0% for VPA <600 mg, 6.1% for VPA 600–1000 mg and 10.4% for VPA >1000 mg [34]. The relative risk increase when comparing the lowest with the highest dose of VPA in the abovementioned studies is 5.8 (95% CI: 3.07–10.92) and 2.2 (95% CI: 1.26–3.82), respectively. More recent reports, with lower numbers, have more variable results. Analyses from Australian Pregnancy Register and Norway registries convey a MCM rate of 13.8% with a RR of 4.23 (95% CI: 1.69–10.57) and 6.3% with a RR of 2.47 (95% CI: 1.58–3.84) [33,35]. Regardless of the exact number, it is now consistently proven that VPA is the most teratogenic AED, with a non-negligible, several-fold increased risk for MCMs when compared with non-exposed controls and LTG, but also to CBZ – with solid prior data supporting this [12]. Although none of the pregnancy registries has sufficient statistical

power to compare specific malformations between all of the different AEDs, VPA is consistently associated with a higher risk of neural tube defects, hypospadias, cardiac defects and oral clefts. As compared with no AED exposure during the first trimester, VPA monotherapy was associated with significantly increased risks for spina bifida, 12.7 (95% CI: 7.7–20.7); atrial septal defect, 2.5 (95% CI: 1.4–4.4); cleft palate, 5.2 (95% CI: 2.8–9.9); hypospadias, 4.8 (95% CI: 2.9–8.1); polydactyly, 2.2 (95% CI: 1.0–4.5) and craniosynostosis, 6.8 (95% CI: 1.8–18.8) in an analysis based on EUROCAT data [41]. The recent UK/Ireland report suggests that the increase in neural tube defects, facial clefts, genitourinary and skeletal malformations were significantly increased for VPA compared with CBZ or LTG, but no significant difference was found for cardiac malformations between CBZ and VPA [34].

Neonatal outcomes are also unfavorable for VPA with a high rate for SGA birth weight (14.5%) and microcephaly (11%) (less than CBZ, but higher than LTG and PHT) in the NEAD study; these rates normalized by 3 years of age [17]. Similarly, data from Danish Medical Birth Registry shows some increase in the SGA rate up to 15.3% [42]. Surprisingly, data from Norway Medical Birth Registry and Finish Medical Birth Register do not show an increased SGA rate for VPA-exposed babies [35,36]. In addition, NEAD study reveals more frequently reduced APGAR scores in the VPA and PHT groups at 1 min, but scores were near-normal in all groups at 5 min. However, the Finnish register found that *in utero* VPA-exposed babies had a greater than twofold increased risk of low 5-min APGAR scores, respiratory treatments, and admission to a neonatal care unit compared with non-exposed controls [36].

Several studies raise the concern for impaired neurodevelopment and long-life cognitive disabilities. The NEAD study was instrumental in determining cognitive abilities after *in utero* exposure to several AEDs, including VPA [20–22]. A more recent study from the UK, with a 46% patient overlap with NEAD, added a control group of women without epilepsy [16]. Meador *et al.* revealed that age-6 years IQ was lower after *in utero* exposure to VPA (mean 97, 95% CI: 94–101) compared with CBZ (105, 95% CI: 102–108; $p = 0.0015$), LTG (108, 95% CI: 105–110; $p = 0.0003$) or PHT (108, 95% CI: 104–112; $p = 0.0006$) [20]. In the NEAD study, children exposed to VPA did poorly on measures of both verbal and non-verbal abilities, but verbal abilities were worse than non-verbal abilities. Memory and executive functions were also inferior when compared with LTG. In the recent Cochrane review meta-analyses, VPA exposure was associated with significantly lower (eight to nine points lower) developmental and intelligence quotients in comparison with control unexposed children as well as children exposed to LTG and PHT [31]. Moreover, higher doses are associated with worse cognitive outcomes and both NEAD and other studies reveal an increased risk for doses approximately 800–1000 mg daily, but currently there are not enough data to determine risk level at specific dose ranges. The recent study from UK confirms previous findings of lower IQ in children exposed to VPA as well as the dose impact [16]. Surprisingly, even if there is little or no reduction in overall IQ in the group with <800 mg/day, there are detectable verbal ability deficits translated into a sixfold increased need for educational intervention, rendering even low-dose VPA treatment unsafe. Moreover, an association with autism spectrum disorder has been reported following VPA *in utero* exposure in several studies, with prevalence estimates ranging from 3 to 15%. The

largest study was conducted by Christensen *et al.*, utilizing electronic healthcare data that included 508 children exposed to VPA, and reported an absolute risk for autism spectrum disorder among children exposed to VPA of 4.42% (95% CI: 2.59–7.46) [43].

VPA is highly protein bound to plasma proteins (90%) and is cleared by beta-oxidation and hepatic metabolism, mainly by glucuronidation through UDP-glucuronosyltransferases (UGT) 1A3 and 2B7 in addition to several CYPs, with <5% excreted unchanged [9,10]. However, given the limited data, free drug monitoring is recommended.

The proportion of WWE who had seizures during pregnancy ranged from 23% for VPA to 31% for LTG in the NAAPR study [3]. The recent Australian Pregnancy Register analysis reports 27% for any seizure and 16.8% for GTCC for WWE on VPA [32]. The updated EURAP analysis reports a rate of 22–32% WWE on VPA having seizures, with only 11.5% experiencing generalized convulsions. VPA also has the lowest rate of seizures during delivery, 1.4%, compared with LTG with the highest rate of 2.6% [5].

Oxcarbazepine (OXC) is a derivative of CBZ. Data so far shows a low MCM rate for OXC, not significantly different from unexposed control groups: 2.2% (OR: 2.0; 95% CI: 0.5–7.4) – NAAPR [3], 2.8% (OR: 0.86; 95% CI: 0.46–1.59) – Denmark [44], 1.8% (OR: 0.64; 95% CI: 0.10–4.61) – Norway [35], 3.3% (6/184) – EURAP [2,29], 1.0% (1/99) – Finland [45]; pooled data from these studies would give a cumulative rate of 2.5%.

Neonatal outcomes are also relatively favorable with one study reporting no fetal growth restriction (Norway [35]) and two others showing a modest increased risk of SGA birth weight (Denmark [42], Finland [36]), one of which also reported an increased rate of elective cesarean sections (Finland [36]). There are no data on the overall neurodevelopment of children who were exposed to OXC *in utero*. However, one study did report a slightly higher rate of autism spectrum disorder, but not autism following OXC exposure *in utero* [43].

OXC is a prodrug, which is rapidly reduced to 10,11-dihydro-10-hydroxy-carbazepine (monohydroxy derivative, MHD), the clinically relevant metabolite of OXC, which is then cleared mainly by glucuronidation. MHD is about 40% bound to plasma proteins. Several studies confirmed that there is a 30–40% decline in MHD serum concentrations throughout pregnancy, likely due to estrogen augmentation of glucuronidation, and an increase of MHD levels within 7–8 days after delivery [10,46]. Thus, OXC needs close plasma level monitoring and dose adjustment.

Reports from NAAPR did bring up one potential concern, in that its efficacy in controlling seizures during pregnancy may be suboptimal, with 43% (78/182) of WWE on OXC monotherapy experiencing seizures during pregnancy [3]. We are limited again, when interpreting this information, by a lack of knowledge about epilepsy type and pre-pregnancy seizure frequency. The increased seizures during pregnancy in this group are likely related to the substantial pharmacokinetic changes during pregnancy, likely due to estrogen augmentation of glucuronidation and increased renal excretion during pregnancy. It is not surprising therefore that the EURAP study group reported that the dosage was increased more often in pregnancies on monotherapy with OXC when compared with other treatments [47].

Lamotrigine is one of the preferred treatments for WWE during their reproductive years. It is a broad-spectrum AED, and it is used extensively to treat bipolar disorder. It is the only newer AED with compelling data with large number of enrolled WWE on LTG in pregnancy registries, as well as its inclusion in the NEAD study, the largest prospective investigation of cognitive outcomes after fetal exposure for several AED monotherapies (CBZ, LTG, PHT and VPA).

The analysis of the NAAPR by Hernández-Díaz *et al.* in 2012 revealed that LTG was already the most commonly reported AED in the Registry, with a MCM rate of 2.0% (95% CI: 1.4–2.8) and a RR 1.8 (95% CI: 0.7–4.6) compared with an unexposed reference group [3], rendering it one of the safest among the commonly prescribed AEDs at that point in time. A more recent study using Australian Pregnancy Register, with a smaller number of pregnancies exposed to LTG, gives a higher MCM rate of 4.6%, but a similar RR 1.4 (95% CI: 0.51–3.80) compared with unexposed pregnancies [33]. The Norway Medical Birth Registry recorded a similar number of 3.4% with a RR 1.26 (95% CI: 0.87–1.84) [35]. A useful observation was reported by the EURAP study group, demonstrating that even for LTG, there is an increased risk with increased dose at the time of conception, and teratogenesis risk doubles with doses >300 mg/day, although with overlapping CIs [2]. Updated observations from the UK/Ireland Pregnancy Register show a similar dose-dependent trend, but with a smaller difference of 1.3% increase in MCM rate for doses >400 mg/day versus <200 mg/day and not statistically significant [34]. Among the MCM observed in LTG-exposed fetuses, there are more cases of cardiac congenital malformation and hypospadias and less of neural tube defects and cleft palate and cleft lip [29]. Note that older studies reporting a high incidence of oral cleft were not confirmed by more recent data, carefully filtered for monotherapy, suggesting that those results were possibly reflecting a contamination with polytherapy data.

Data from the Finnish Medical Birth Register suggest that full-term offspring exposed to LTG monotherapy were at an increased risk of admission to a neonatal care unit when compared with offspring of non-exposed women [36]. Regarding neonatal outcomes, the NEAD study found no risk for SGA birth weight, although it showed a mild increase in microcephaly rates for LTG-exposed babies (9%). This was less than that observed for CZB and VPA; it attenuated by 24 months and normalized by 36 months. Moreover, it did not impact cognitive outcomes, assessed at age 3 years [17].

The NEAD study also raised the concern that verbal abilities were worse than non-verbal abilities in LTG-exposed children and that cerebral lateralization may be affected, as right-handedness was less frequent than expected in the LTG-exposed children. A relationship between the dose and child's neurodevelopment was not found. Baker *et al.* found that the children exposed to LTG *in utero* did not have significantly lower IQ or specific verbal, non-verbal or spatial abilities in comparison to control children [16]. One study that explored the rates of autism spectrum disorder in children exposed to LTG *in utero* found an increase from 1.8% in the general population to 3.3% in the exposed group, but findings were not significant and numbers were small (30 total LTG exposures) [23].

LTG has complicated pharmacokinetics and needs close monitoring of drug level and dose adjustment during pregnancy. It is 55% protein-bound and undergoes liver metabolism by UGT1A4 and likely other UGT enzymes. It is hypothesized that the rising levels of estrogens during pregnancy may induce the UGT enzyme system and consequently increase the metabolism of LTG leading to decreases in LTG concentrations. The majority of women experience a significant increase in clearance and a decrease in serum concentrations, requiring frequent dose adjustment [48]. In a class I study with a prospective, observational design, Pennell *et al.* demonstrated that both LTG total and free clearance increased throughout pregnancy with a peak of 94% (total) and 89% (free) in the third trimester [49]. Therefore, the authors concluded that monitoring of total levels was sufficient without the need for free level measurements. This study also demonstrated that use of an empiric postpartum taper schedule of LTG over 10–14 days reduced the occurrence of postpartum toxicity. A subsequent study with more formal pharmacokinetic modeling demonstrated that a subgroup of women (23%) experienced a minimal increase in clearance, likely secondary to genotypic variations in the activity or induction of UGT1A4, while the remaining 77% experienced a greater than threefold increase in clearance, with return to baseline clearance over 3 weeks. The individual variation emphasizes the need for therapeutic drug monitoring during pregnancy [48].

There are studies raising the concern that although LTG is associated with one of the most benign teratogenic profiles, it may be associated with a relatively high risk for seizure worsening if therapeutic drug monitoring and/or dosage adjustments are not employed during pregnancy. In the NAAPR, approximately 30% of women on LTG or LEV monotherapy had seizures during pregnancy [3]. Data from the Australian Pregnancy Register reported that approximately 50% of women on LTG experienced seizures during pregnancy [32]. The EURAP study did not detect initially a difference in the seizure control among the AEDs compared [2], but revised data with a focus on seizure control reported that WWE on LTG during pregnancy had more seizures overall (42%), more GTCC (21%), a greater likelihood of deterioration in seizure control from first to second or third trimesters (20%) and seizure during delivery (2.6%), and were more likely to require an increase in drug load (48%) [5]. However, some of these findings may be secondary to LTG pharmacokinetics and inadequate dose correction during pregnancy. In addition, WWE on LTG <300 mg/day at the time of conception had a better seizure control profile compared with those on higher doses, suggesting that the data are likely to reflect more the epilepsy severity rather than LTG efficacy. The same studies carefully characterizing the drug pharmacokinetics demonstrated that, with the use of therapeutic drug monitoring, the percent of WWE on LTG mono-therapy with seizure worsening during pregnancy was similar to that reported with other AEDs considered more stable for seizure control [48,49]. Furthermore, they were able to demonstrate that seizure frequency increased when the LTG level decreased to 65% of the preconceptional individualized target LTG concentration. Another study but with a retrospective approach found that for all monotherapies, seizures worsened significantly when the AED blood concentrations fell to <65% of preconception baseline [28]. The minimal goal of therapeutic drug monitoring with LTG should be to maintain the LTG concentration during pregnancy above 65% of the preconception baseline.

Gabapentin (GBP) is structurally similar to the inhibitory neurotransmitter gamma amino butyric acid (GABA) and is used to treat seizures with a focal onset in adults and children.

The data on MCM rates so far are promising, but the numbers are quite low and do not provide tight confidence intervals. MCM reports by registry are 1/145 (OR: 0.6 compared with unexposed controls; 95% CI: 0.07–5.2) in NAAPR [3]; 0/23 in EURAP [2]; 0/39 in Norway [35]; 1/59 (OR: 0.53 compared with unexposed controls; 95% CI: 0.07–3.85) in Denmark [42]; 0/14 in the Australian Pregnancy Register [33]; 1/31 (3.2%) in the UK/Ireland Register [50] and 1/17 (5.9%) in the Gabapentin Pregnancy Registry [51]. Pooling the data from all of these studies leads to MCM rate of 1.2%.

Recent data from Danish Medical Birth Registry provides information about neonatal outcomes from 72 pregnant women on monotherapy with GBP and reveals an increased risk of SGA birth weight to 12.5%, but it did not reach statistical significance [42]. Another study suggests a trend toward premature birth and low birth weight, but findings are confounded by polytherapy with other AEDs and psychotropic medications [52]. No data are yet available on the impact of *in utero* exposure to GBP on long-term neurodevelopment or autism.

GBP has good oral bioavailability, but only up to certain doses as saturation occurs at higher doses; it is not bound to serum proteins, not metabolized by the liver and it is eliminated by renal excretion. Despite increased glomerular filtration during pregnancy, and expected fall in GBP plasma concentration, the reported few cases do not suggest major variations [53], but more data are needed on serum concentrations throughout pregnancy to accurately characterize the pharmacokinetics of GBP.

Little information is available on its efficacy in controlling seizures during pregnancy, but limited data from NAAPR suggest that a relatively high percentage (45%) of WWE on GBP monotherapy have seizures during pregnancy [3].

Topiramate is a second-generation AED, with an indication for treatment of epilepsy and migraine and, more recently, morbid obesity. Its use among WWE of childbearing age has been increasing considerably in the past decade and thus more data are now available on its efficacy in controlling seizures and impact on *in utero*-exposed fetuses.

The rate of MCM has been consistently higher than for other newer AEDs in most studies: NAAPR data revealed a MCM rate of 4.2% (15/359; OR: 3.8; 95% CI: 1.4–10.6) [3] and EURAP of 6.8% (5/73) [2]; the Danish Medical Birth Registry analysis revealed a MCM rate of 4.6% (5/108; OR: 1.44; 95% CI: 0.58–3.58) [44] and a recent study using Norway Medical Birth Registry data reported a MCM rate of 4.2% (2/48; OR: 1.66; 95% CI: 0.40–6.85) but had low numbers [35]; while the Australian Pregnancy Register data with similarly low numbers revealed a lower rate of 2.4% (1/42; OR: 0.73; 95% CI: 0.09–6.07) [33]. The 2012 NAAPR analysis revealed a higher number of oral clefts, consistent with prior publications and data from animal studies. There were a few hypospadias and cardiac malformations, but no neural tube defects [3]. A more recent retrospective cohort study supports an increased risk of oral clefts, with a prevalence ratio of 5.4 (95% CI: 2.0–14.6) in the TPM cohort compared with non-exposed controls [54]. Similarly, an earlier study

reporting results from the Slone Epidemiology Center Birth Defects Study (1997–2009) and the National Birth Defects Prevents Study (1997–2007) showed comparable numbers with a prevalence ratio for oral clefts of 5.4 (1.5–20.1) [55].

Adverse neonatal outcomes are another concern with use of TPM during pregnancy. Recent data from NAAPR suggest an increased risk of SGA of 17.9% for TPM (compared with LTG, RR: 2.4; 95% CI: 1.8–3.3), with a mean lower birth weight of 221 g, respectively, and a mean lesser neonatal length of 1 cm as compared with LTG exposure ($p < 0.01$) [56]. Another study from 2014, from Norway, with smaller numbers, raises the same concern that TPM is associated with a considerable risk of microcephaly and SGA birth weight [35].

Regarding neurodevelopmental outcomes, so far, only one study investigated the abilities of children exposed to TPM *in utero* and reported a significant difference between the children exposed to TPM in comparison to control children [57]. This was a small study though and more data are needed before concluding about the risk of neurodevelopmental harm with TPM therapy.

TPM has good bioavailability, only 15% is bound to plasma proteins, 20–30% is metabolized and the rest is eliminated unchanged through the kidneys [10,58]. Given the increased renal blood flow during pregnancy, and subsequent increased TPM clearance, serum TPM concentrations can drop up to 40% during pregnancy [10]. Thus, serum level monitoring should be considered and the dose may need adjustment during pregnancy and after delivery.

From the NAAPR data published in 2012 [3] revealing that 33% (100/359) WWE on TPM had seizures during pregnancy, to the recent update focused on TPM [56] revealing 32.2% (91/347) had seizures, and the Australian Pregnancy Register [32] reporting rates of 54.8% of women having seizures and 33.3% convulsive seizures, women on TPM do not have optimal seizure control during pregnancy. Again, this could reflect that practitioners are choosing TPM for women that have more medically refractory epilepsy and thus direct comparisons to reports on other AEDs cannot be made.

Levetiracetam is a newer AED with a limited side-effect profile and simple pharmacokinetics, suitable for both focal onset and generalized epilepsies. It has become one of the AEDs of choice for WWE of childbearing age [32,59], particularly for those with idiopathic generalized epilepsy syndromes, given that the alternative, VPA, has been repeatedly demonstrated to have detrimental effects on the fetus.

Chaudhry *et al.* [60] reviewed the literature and included eight studies: five pregnancy registries (The North American AED Pregnancy Registry (NAAPR) [3]; the UK and Ireland Epilepsy and Pregnancy Registers [59], the International Registry of Anti-epileptic Drugs and Pregnancy (EURAP) [2], the Australian Pregnancy Register [19], UCB Antiepileptic Drug Pregnancy Registry and a Danish population-based cohort [44]) and one population-based cohort study that analyzed the congenital malformation rate as well as two studies investigating neurodevelopment in LEV-exposed children. They showed that the overall congenital malformation risk for children of WWE on LEV is 2.2% (95% CI: 1.53–3.22), but when limited to MCMs (excluding birth marks, positional deformations and minor

anomalies), the rate was only 1.7% (95% CI: 1.14–2.63), not significantly different from children of WWE on no AEDs and the general population (1–3%). This is in agreement with recently revised data from Australian Pregnancy Register [33] and Medical Birth Registry of Norway (MBRN) [35]. Neither the UK and Ireland Epilepsy and Pregnancy Registers nor the NAAPR found an association between the dose of LEV and MCM rate, although the former suggests a trend given that the mean dose associated with MCM (3000 mg) was nearly double that used in those with normal pregnancy outcomes ($p = 0.09$).

The UK/Ireland Epilepsy and Pregnancy Register is the register that in the past raised concern for potentially low birth weight after exposure to LEV; however, a more recent study refuted this association [59]. Similarly, the MBRN reports no risk of growth restriction for LEV, with a rate of SGA birth weight or head circumference similar to that for the normal population [35]. This is in contrast with data from Finland, a report with lower numbers (56 total, 12 monotherapy exposed pregnancies), which raised the concern that LEV use may lead to increased risk of caesarean sections and a more than twofold increased risk of preterm birth and more than threefold increased risk of low birth weight compared with offspring of non-exposed women [36], although this holds true only when the analysis includes polytherapy and not monotherapy cases.

Regarding developmental outcomes, data from the same UK/Ireland Epilepsy and Pregnancy Register suggests that *in utero* exposure to LEV does not have adverse effects on neurodevelopment – tested on children at 24 months [26] and at 3–4 years of age [26]. There is no study in the literature to suggest a correlation between autism spectrum disorders and *in utero* exposure to LEV.

Pharmacokinetic studies of LEV have shown the need to monitor the levels closely during pregnancy and after delivery because of ample clearance changes. LEV has complete oral bioavailability, with no binding to plasma proteins and no hepatic metabolism, approximately 30% being metabolized by hydrolysis and the rest eliminated primarily unchanged via renal excretion. Significant changes in clearance during pregnancy were observed for LEV with an up to twofold increase from non-pregnant baseline. This leads to a decline in serum concentration by 40–60% compared with baseline levels prior to pregnancy and a need to increase the dose by 40% by the end of pregnancy to maintain baseline serum concentrations [28]. However, the dose needs to be readjusted after delivery given the rapid increase in serum concentrations within the first week postpartum [10].

There are also recent data about efficacy for controlling seizures during pregnancy with a seizure occurrence rate of 30–40% in different studies: 30% (NAAPR) [3], 31.7% (Australian Pregnancy Register) and 38.2% (UK/Ireland Epilepsy and Pregnancy Register) [32] for any seizures. For convulsive seizures, the percentages reported are around 15%: 13.4% (Australian Pregnancy Register) and 17.8% (UK/Ireland Epilepsy and Pregnancy Register) [59], similar to the overall rate for all older AEDs. Given substantial pharmacokinetic changes in pregnancy for LEV, seizure worsening may be correlated with unadjusted drops in LEV level. Reisinger *et al.* demonstrated that, if drug level fell 35% from preconception baseline, seizures worsened significantly during the second trimester even when controlling for seizure occurrence in the year prior to conception [28].

Zonisamide (ZNS) is a broad-spectrum AED and is used for both focal-onset and generalized seizures, often as adjunctive treatment. The NAAPR group reported a ZNS monotherapy MCM rate of 0% (0/90) in 2012, albeit with modestly low number of exposures [3].

Similar to TPM, in adults taking the medication, it can cause major weight loss. There is no study addressing whether this has an impact on maternal weight during pregnancy, but we do have information on fetal growth. Analyzed in parallel with TPM in a recent study using NAAPR data, ZNS was also associated with an increased rate of SGA of 12.2% with an OR 2.2 (95% CI: 1.1–4.4) compared with the unexposed control group, but not significant when compared with LTG-exposed group (RR: 1.6; 95% CI: 0.9–2.8) [56].

There are no data on the impact on cognitive abilities of children exposed *in utero* to ZNS.

The pharmacokinetics of ZNS during pregnancy are insufficiently studied. It is approximately half bound to serum proteins and extensively metabolized by acetylation, glucuronide conjugation and oxidation, and is 15–30% is eliminated by renal excretion [10,46]. A couple of case reports suggest the possibility of increased clearance during pregnancy, but more data are needed to draw conclusions on its gestation-related alterations in pharmacokinetics and clinical impact. Very limited data are available for its efficacy for seizure control in pregnancy. One study, using the NAAPR data, reports that 19.6% (19/97) of WVE on ZNS monotherapy had seizures during pregnancy [56].

Other second-generation AEDs, such as felbamate, pregabalin, tiagabine and vigabatrin have a even lower prescription rates in adults with epilepsy and their effect on pregnancy is not well defined.

Third-generation AEDs: lacosamide, eslicarbazepine, retigabine/ezogabine, perampanel. There are little data on the use of third-generation AEDs during pregnancy. One study mentions an accidental pregnancy in one patient who had received approximately 6 months of perampanel therapy and was discontinued from treatment following confirmation of pregnancy. Per report, the patient delivered a healthy, full-term infant [61].

Monotherapy versus polytherapy

Review of literature by a committee of experts in 2009 led to the publication of practice parameter updates in Neurology, recommending avoidance of AED polytherapy in pregnancy and use of AED monotherapy [12]. Since then, several studies seem to indicate that rather than polytherapy *per se*, it is the inclusion of certain AEDs – VPA, in particular – that lead to poorer MCM outcomes. Data from Australian Pregnancy Register published in 2010 suggested that the fetal hazard of AED polytherapy relative to monotherapy depends on the degree of exposure to VPA [62]. In 2011, NAAPR data revealed similarly that LTG plus VPA has a higher rate of MCM than LTG alone, but it also showed that the rate for the combination of LTG plus CBZ is close to that of LTG monotherapy [58,63]. More recent data from Australian Pregnancy Register incriminates TPM as another agent that, when used in polytherapy, increases the risk for MCM [33]. Data from Norway seems to indicate a

similar trend for minimal increase in the rate of MCM for polytherapy with ‘newer’ AEDs, except TPM, which similar to VPA, seemed to elevate the MCM rate [35].

Despite emerging data clarifying MCM rates for certain polytherapy combinations, little information is available about other obstetrical, neonatal and neurodevelopmental risks. One retrospective study on a large number of children (1235) exposed to AEDs, mainly CBZ or PHT, showed that children exposed to polytherapy had an increased risk of poor performance in school [64]. In this study, not receiving a final grade was measured and felt to reflect that the child had not attended the lectures in that subject enough to get a grade, suggesting that the child had gone to special schools for children with static encephalopathy. In this study, children exposed to poly-therapy had an increased risk of not receiving a final grade (OR: 2.99; 95% CI: 2.14–4.17), while children exposed to monotherapy did not have a significantly increased risk of not receiving a final grade (OR: 1.19; 95% CI: 0.79–1.80). Overall, polytherapy AED use appears to confer a higher risk for neurodevelopmental delays [12]. The risk of AED polytherapy for these other outcomes includes exposures across all three trimesters. Recent EURAP data analysis reveals that 2.6% of WWE had another AED added to the initial monotherapy for better seizure control and this measure was more often taken for pregnancies with seizures during the first trimester. Adding a second AED was more common among LTG pregnancies (4.6% 58/1251; $p < 0.0001$) [5]. Thus, we need to have a better understanding about particular drug combinations to be able to make the right clinical decision.

Expert commentary

There is a large body of data on monotherapy use of older AEDs: VPA, phenobarbital, PHT, CBZ as well as some of the second-generation AEDs: LTG and LEV. There is increasingly more information published on other second-generation AEDs: OXC, TPM, ZNS and GBP. However, we do not have data on the other second-generation AEDs nor on any of the third-generation AEDs. Given the data we have thus far, mainly based on MCM rate, but also considering the limited data on neonatal and neurodevelopmental outcomes, the preferred AEDs during pregnancy, in decreasing order, are: LEV and LTG, followed closely by CBZ and, with less data, but similar MCM safety, OXC. There is a reasonable amount of data for PHT and PB, but these AEDs have slightly higher risks during pregnancy. There are limited data on GBP and ZNS to determine exactly where they would fit in this ranking and, although they show a low MCM risk, ZNS, in particular, may be associated with higher rates of SGA births. TPM, a drug with expansive use in the past decade is likely to fall out of favor given reproducible evidence of increased MCM rate, low birth weights and potential neurodevelopmental problems. VPA should be viewed as a last resort AED choice only after other AEDs have failed, given increased MCM rates, worse neonatal outcomes and detrimental impact on long-term neurodevelopment, including increased rates of autism.

In terms of efficacy for different AED monotherapies during pregnancy, there is no study addressing this question. Pregnancy registries gather very limited data and offer only % of WWE that have seizures during pregnancy. This information is hard to interpret given the lack of detailed information about the variety of seizure types and epilepsy syndromes with variable severities, as well as lack of knowledge about pre-pregnancy seizure frequency,

AED levels or dose adjustment during pregnancy. Moreover, pregnancy impact on pharmacokinetics for each AED is variable and drug levels are not always monitored for dosage adjustments, leading to another confounding factor when interpreting seizure frequency. A thorough retrospective study found that for all monotherapies, seizures worsened significantly when the AED blood concentrations fell to <65% of preconception baseline [28].

There may be variations in seizure control during pregnancy dependent on AED monotherapy used, beyond just those triggered by different pharmacokinetics. However, assessing efficacy is not possible at the moment in light of the fact that these pregnancy registries are not able to provide detailed information about non-pregnant baseline seizure frequency and types, epilepsy syndromes, AED levels and detailed dosage adjustments.

Five-year view

While a lot of progress has been made in understanding how epilepsy and its management impact pregnancy and child outcomes, there are still many unknowns. First, the information about teratogenicity is robust for older AEDs, but it is still incomplete for newer drugs. Second, there is a limited, but growing body of information about neonatal outcomes with little if any data on obstetric outcomes. Regarding neurodevelopmental impact, the groundwork done by the NEAD study informs us of long-term behavioral and cognitive outcomes for some commonly used AEDs; its continuation, the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study is meant to further our knowledge about many maternal and child outcomes, including the neurodevelopmental impact of using a variety of AEDs and in various combinations during pregnancy and breastfeeding [28]. Finally, “exposure” is loosely defined and most studies do not have a quantitative measure for the degree of exposure. Even when this is attempted, the dose of AED is taken into consideration, which is likely a poor surrogate given the extent and inter-individual variability in pharmacokinetic changes during pregnancy and placental passage rates. The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs study will try to address this question in a more rigorous fashion by determining the amount of exposure to the mother and child through measurement of the medicine concentration during pregnancy, in the umbilical cord blood at birth and during postpartum and breastfeeding.

Another important question is that of polytherapy. Recent studies have started to challenge the dogma that monotherapy is always better than polytherapy, but given the low numbers of exposures, not many combinations have been analyzed in adequate detail. One thing seems to be certain: excluding VPA from the combination will allow for better MCM outcomes. As a significant fraction of WWE need more than one AED to control their seizures, we need to gather more data to provide evidence-based guidelines to our patients when choosing different combinations.

Through the work of many passionate clinicians and researchers, this body of information is growing and will continue to further our knowledge on the impact of AEDs on the mother and child, will clarify unanswered questions about AED pharmacokinetics and will allow for better medical guidance at this important time in the life of WWE.

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Key issues

- Seizure freedom rate during pregnancy is higher in women with epilepsy (WWE) with generalized epilepsies (73.6%) than in those with localization-related epilepsy (59.5%).
- Seizure control prior to pregnancy is the best predictor for seizure control during pregnancy: approximately 90% of WWE remain seizure-free during pregnancy if seizure-free for at least 9 months to 1 year prior to pregnancy, while WWE who had seizures in the pre-pregnancy month had 15-times higher risk for seizures during pregnancy.
- A parental history of major congenital malformations (MCM) increases its risk more than fourfold; a history of fetal malformations in a previous pregnancy on the same antiepileptic drug leads to more than 15-fold increased risk.
- Based on clinical evidence so far, levetiracetam and lamotrigine seem to have the safest profile for MCM risk, neonatal and neurodevelopmental outcomes.
- Valproate is recommended to be used only as a last resort after other antiepileptic drug trials have failed, given increased MCM rates and detrimental impact on long-term neurodevelopment, including increased risk for autism.
- Topiramate should also be used cautiously given reproducible evidence of increased risk for MCM, fetal growth restriction and potentially negative impact on neurodevelopment.
- If polytherapy is necessary, the MCM outcomes are likely to be better if the combination chosen does not include valproate or topiramate.

Figure 1.
Complex relationship between pregnancy, epilepsy and its treatment.

Table 1.
Available antiepileptic drugs, their use and interaction with sex hormone metabolism/oral contraceptive pill.

	Year of introduction			Indication and efficacy in treating seizure disorders			Degree of induction of sex steroid hormone metabolism/OCP	
	USA	Europe	Focal onset with or without secondary generalization	Primarily generalized seizures		Other seizure types	Status epilepticus	Strong (++) Weak (+) Non-inducers (-)
First-generation AED								
Bromides	1857	1857	Withdrawn in 1975					N/A
Phenobarbital	1912	1912	Yes	Yes			Yes	++
Phenytoin	1937	1939	Yes	Yes			Yes	++
Primidone	1954	1953	Yes	Yes			No	++
Ethosuximide	1960	1958	No	Yes		Absence, CSWS	No	-
Carbamazepine	1974	1965	Yes	No			No	++
Clonazepam/Benzodiazepines	1975	1971	Yes	Yes			Yes	-
Valproate	1978	1970	Yes	Yes			Yes	-
Second-generation AED								
Vigabatrin	2009	1989	Yes	No		Infantile spasms	No	-
Felbamate	1993	1994	Yes	Yes		Severe refractory epilepsy only	No	+
Gabapentin	1993	1994	Yes	No			No	-
Lamotrigine	1995	1991	Yes	Yes			No	+
Topiramate	1997	1995	Yes	Yes			No	+
Tiagabine	1997	1996	Yes	No			No	-
Levetiracetam	1999	2000	Yes	Yes		Myoclonic	Yes	-
Pregabalin	2005	2005	Yes	No			No	-
Oxcarbazepine	2000	1990	Yes	Yes			No	++
Zonisamide	2000	2007	Yes	Yes		Infantile spasms, myoclonic	No	-
Stiripentol	N/A	2007	No	Yes		Myoclonic	No	-
Rufinamide	2008	2007				LGS		+
Third-generation AED								
Eslicarbazepine	2013	2010	Yes	Yes			No	+
Lacosamide	2009	2010	Yes	No			Yes	-

Year of introduction		Indication and efficacy in treating seizure disorders		Degree of induction of sex steroid hormone metabolism/OCP	
USA	Europe	<i>Focal onset with or without secondary generalization</i>	<i>Primarily generalized seizures</i>	<i>Other seizure types</i>	<i>Status epilepticus</i>
				<i>Strong (++)</i> <i>Weak (+)</i> <i>Non-inducers (-)</i>	
Clobazam	2011	Yes	Yes	Myoclonic, absence	No
Retigabine	2010	Yes	No		No
Perampamel	2012	Yes	Yes	Refractory	No

AED: Antiepileptic drug; CSWS: Continuous spikes and waves during sleep; LGS: Lennox-Gastaut Syndrome.

Table 2.

Data on individual antiepileptic drug efficacy in controlling seizures, impact on fetal growth and neurodevelopment, obstetrical outcomes and pharmacokinetics.

AED	PB	PHT	CBZ	VPA	oxc	LTG	GBP	TPM	LEV	ZNS
MCM rate	(dose dependent)		(dose dependent)	(dose dependent)		(dose dependent)				
%	6–7%	2.4–7%	3–8.7%	9–10%	1–3.3%	2–4.4%	0–5.9%	2.4–6.8%	0.7–2.4%	0%
RR to LTG [3]	2.5	1.5	1.5–4.6	5.1	1.1	Reference	0.3	2.2	1.2	N/A
Most frequent MCM (cardiac [C], oral clefts [OC], spina bifida [SB], urogenital [UG])	C and OC	C	None	SB	None	C and UG	None	OC	None	N/A
<i>Neonatal outcomes</i>										
SGA BW	N/A	No	12.9% [17]	14.5% [17]	16% [42]	No [17]	12.5% [42]	17.9% [56]	No	12.2% [56]
SGA HC	N/A	8% [17]	19% [17]	11% [17]	N/A	9% [17]	N/A	14.9% [35]	No	N/A
Others (LBW, APGAR, ICU stay, perinatal death, etc.)	N/A	N/A	Reduced APGAR score at 1 min (RR 2.0) Increased risk of respiratory treatment Increased risk of admission to a neonatal unit Increased risk of perinatal death (RR 1.9) [5]	Reduced APGAR score (RR ~2.7) [5,17] Increased risk of admission to a neonatal unit (RR ~2.6) [5]	N/A	Increased risk of admission to neonatal unit (RR ~2.0) [5]	N/A	N/A ^f	No	N/A
Obstetrical outcomes (Preterm, CS)	N/A	Favorable	Increased risk of preterm birth, LBW [36]	Favorable	Increase in elective C-section[36]	Favorable	N/A	N/A	Favorable	N/A
<i>Neonatal outcomes</i>										
IQ	N/A	No reduction	No reduction	8–9 points lower	N/A	No reduction	N/A	Possible negative	Limited data reveal no	N/A
Specific cognitive abilities impaired	N/A	Concern for lower memory index, poor verbal abilities, delayed motor development	Concern for poor verbal abilities	Verbal, memory and executive abilities	N/A	Concern for verbal ability impairment	N/A	impact [57]	negative impact [25,26]	N/A
Need for educational support	N/A	Unknown [20–22]	Unknown [8–10]	Likely [20–22]	N/A	Unknown [20–22]	N/A			N/A
Relation to ASD (Note: Prevalence of ASD in the general population is 1.8%) [31]	None reported	None reported	No significant increase in ASD	Increased prevalence (3–15%)	None reported	Increased autistic traits reported by 2 studies with small n	None reported	None reported	None reported	None reported

AED	PB	PHT	CBZ	VPA	oxc	LTG	GBP	TPM	LEV	ZNS
Expected plasma concentration variation [9,10]	Up to50% decrease	16–49% decrease	Increase in the free fraction	Up to 50% decrease	30–40% decline	Up to 60% decrease	Little variation reported	Up to 40% decrease	Up to 60% decrease	Insufficient data
Need for monitoring AED plasma levels	Yes	Yes	No	Yes	Yes	Yes	Recommended	Yes	Yes	Yes
<i>Reported seizure frequency during pregnancy</i>										
% any seizure	26.6 [5]	27.2 [3]	32.7 [5]	25.0 [5]	43.6 [3]	41.8 [5]> 29.1 [3]	44.8 [3]	32.2% [3]	30.9 [3]	19.6 [3]
% GTCC	14.0 [5]	N/A	12.6 [5]	11.5 [5]	N/A	21.1 [5]	N/A	N/A	N/A	N/A

Data on individual AED regarding major malformation rate (MCM), impact on fetal growth – small for gestational age (SGA) birth weight (BW) and head circumference (HC), obstetrical outcomes – including preterm delivery and Caesarian section (CS), neurodevelopment – intelligence quotient (IQ) and relation to autism spectrum disorder (ASD), pharmacokinetics and reported seizure frequency - for any seizure or generalized tonic-clonic convulsion (GTCC).