Epilepsy and pregnancy: What should the neurologists do?

S. Dupont, L. Vercueil

Epilepsy and pregnancy: what should the neurologists do?

Dupont S[1,2,3], Vercueil L[4]

[1]Epilepsy and Rehabilitation Unit, Hôpital de la Pitié-Salpêtrière, APHP, Paris, France

[2]Centre de Recherche de l'Institut du Cerveau et de la Moëlle Epinière (ICM), UMPC-UMR 7225 CNRS-UMRS 975 INSERM, Paris, France

[3] Université Paris Sorbonne, France

[4]EFSN, Univ. Grenoble Alpes, Inserm, U1216, CHU Grenoble Alpes, Grenoble Institut Neurosciences, GIN, 38000 Grenoble, France

Correspondance :

Pr S Dupont, Unité d'Epilepsie

Hôpital de la Salpêtrière

47, boulevard de l'Hôpital

75651 Paris cedex 13, France

Phone: (33) 1 42 16 41 15

FAX: (33) 1 42 16 03 03

E-mail : sophie.dupont@psl.aphp.fr

Abstract

Epilepsy is one of the most common chronic disorders affecting women of childbearing age. Unfortunately, many women with epilepsy (WWE) still report not receiving key information about pregnancy. They obviously need information about epilepsy and pregnancy prior to conception with a particular emphasis on effective birth control (i.e contraception), necessity to plan pregnancy, antiepileptic drugs optimization, and folate supplementation. The risks associated with use of antiepileptic drugs during pregnancy has to be balanced against fetal and maternal risks associated with uncontrolled seizures.

This report reviews evidence-based counseling and management strategies concerning maternal and fetal risks associated with seizures, teratogenic risks associated with antiepileptic drug exposure with a special emphasis on developmental and behavioural outcomes of children exposed to intra utero antiepileptic drugs.

Key words: pregnancy, epilepsy, counselling, education

Abbreviations: woman with epilepsy =WWE, AED =antiepileptic drug, **network meta-analysis = NMA**

Disclosures: Authors report no disclosures relevant to the manuscript.

Pregnancy should be a concern and a topic of discussion with any woman of childbearing age who has epilepsy. It is crucial for patients and neurologists to plan ahead for a possible pregnancy, as soon as possible. One of the priority objectives is to provide all the information necessary for the project, even if it is still distant. There are still misconceptions about this situation that can have a negative impact on people [1]. Women and future parents must know both what is possible and what the constraints that may weigh on this project are.

In this article we will review the current data concerning the risks of carrying a pregnancy with epilepsy and antiepileptic drugs. However, we will also insist on the need to prepare young girls as soon as possible for this eventuality, by emphasizing the imperative of anticipating any pregnancy. Finally, we will also address the postpartum period, with the need to better manage the risk of significant fragmentation of the mother's sleep, and to correct the prescribed dosages.

Neurologists should feel deeply involved in the care of women with epilepsy, especially regarding the four issues discussed below: they should anticipate pregnancy, consider the risk of seizures during pregnancy, manage the risk of fetal complication related to antiepileptic drug use and anticipate delivery and breast feeding.

1- Anticipate Pregnancy

It is important to remind the young girl, even long before the project takes shape that epilepsy is in no way a contraindication to pregnancy. There are unfortunately still women who believed that the presence of their epilepsy definitively prevented them from having a married life, marital projects and children. Being able to plan and properly supervise a pregnancy in a woman with epilepsy (WWE) will depend on her previous information. Addressing the issue early in life, for example during adolescence, is therefore important. Preconception counselling is arguably the most important information a WWE receives in order to minimize the teratogenic risk of antiepileptic drugs (AEDs) and optimize seizure control prior to getting pregnant. Thus, understanding and obtaining an optimal form of contraception is an important part of their health management early in their care.

Contraception counseling

Which contraception for women with epilepsy?

The choice of a contraceptive drug can be challenging for WWE due to possible interactions between AEDs and hormonal contraception.

Five categories of AEDs may be considered:

- Classical enzyme inducing AEDs such as phenobarbitone, phenytoin, carbamazepine, and at a lesser degree oxcarbazepine, and eslicarbazepine: they increase the metabolism of orally administered estrogen and progesterone to a lesser extent. Combined estrogen and progestin contraceptives, progestin-only pills and subdermal progestogen implants are therefore likely to be ineffective, and are not recommended in those patients on enzyme inducing AEDs [2]. Hormonal patch and vaginal rings are also prohibited.
- Dose-dependent enzyme inducing AEDs: Topiramate over 200 mg/day [3] and perampanel at 12 mg/day [4] are less potent inducers but may alter plasma concentrations of hormonal contraceptives to some degree. Local or oral hormonal contraception is therefore not recommended.
- Enzyme-inducer AED for hormonal contraception:
    - Felbamate decrease plasma concentrations of hormonal contraceptives and carbamazepine but increase plasma concentrations of phenytoin, valproic acid or the epoxide metabolite of carbamazepine [5,6]. There again, local or oral hormonal contraception is not recommended.
    - Rufinamide is not an enzyme-inducer AED but was shown to decrease the exposure to both ethinyl oestradiol and norethindrone at high dose (1600 mg/day), the mechanism of interaction has not been established and lower dosages have not been tested [7]
- Enzyme inhibitor: valproate doesn't alter the metabolism of orally administered estrogen and progesterone
- Neutral AEDs: available data, although sparse, suggest that gabapentin, pregabaline, levetiracetam, brivaracetam, zonisamide, lamotrigine and lacosamide do not affect the metabolism of oral contraceptives. Perampanel up to 10 mg/day appears also safe (see table 1).

Depot medroxyprogesterone-acetate (MPA) injections appear to be effective for all AEDs categories, however they may not be first choice due to serious side effects (delayed return to fertility, impaired bone health).

This potential complex interactions between oral contraception and AEDs led the World Health Organization to recommend avoiding combination contraceptive pills containing estrogen and progesteron in WWE who desire contraception. They recommend at first choice the use of intrauterine devices as an alternative method of contraception in the majority of WWE, with the advantage of no relevant drug-drug interactions. The levonorgestrel intrauterine system appears to be effective, even in women taking enzyme inducing AEDs and seems as well tolerated in WWE than in women without epilepsy [8]. In a recent study, Herzog et al. demonstrated that among reversible contraceptives, intrauterine devices had the lowest failure rate. Oral hormonal contraceptives had a higher failure rate, especially if combined with enzyme-inducing AED. As in the general population, failure rates were higher in younger, racial minority, and Hispanic WWE [9].

Bidirectionnal link between contraception and AEDs

Estrogen can increase the metabolism of certain AEDs, such as lamotrigine or at a lesser extent valproate, leading to cyclical variation in its blood level with resultant adverse effect profile or seizure dyscontrol. In literature, both lamotrigine and valproate serum concentrations are reduced when ethinyl estradiol is taken concomitantly, presumably due to accelerated glucuronidation [10-12]. The clinical relevance of the modest effect on valproate is unclear and seems meaningless. However, lamotrigine serum concentrations may decrease by more than 50%, and therapeutic failure in the form of increased seizure frequency/recurrence of seizures has been reported. It is therefore recommended to dose lamotrigine serum concentration before and after the introduction of an oral combined contraception.

Concerning progesterone, a recent study suggests that drospirenon and levonorgestrel but not gestoden may reduce lamotrigine serum concentrations when being co-administered in WWE which might be of importance concerning seizure risk. Vice versa, no effect of LTG on several progestins could be demonstrated, arguing against a potential loss of contraception safety with lamotrigine [13].

Unintended pregnancies: a need for a better contraceptive counselling

A prospective population based study performed in Newcastle in 2000 demonstrated that less than 50% of pregnancies were planned, partly because of oral contraceptive failure [14]. Nine years later, an American study showed that 65% of WWE receiving enzyme inducers AEDs were unaware of a decrease in oral contraception efficacy and, there again, women reported that 50% of their pregnancies were unplanned [15]. In 2017, one study of 1,144 WWE who self-enrolled in a birth control registry and completed a retrospective survey found that 65% of reported pregnancies in WWE were unintended [9]. Several causes were found to explain this high proportion of unintended pregnancies: i) 30.3% of WWE were using contraceptive methods that are not considered to be highly effective in the general population (withdrawal, barrier, or combinations thereof), ii) there was an additional 14.5% who used systemic hormonal contraception in combination with an enzyme-inducing AED which can compromise contraceptive efficacy and finally 34.7% of unintended pregnancies in this WWE population occurred on no contraception. Another study performed in 2018 in a population including both WWE (n=541) and women without epilepsy (n=73619) found that in WWE, 55% of pregnancies were unintended compared to 48% in women without epilepsy. Maternal age and socioeconomic status differences likely contribute to the higher rates in WWE compared to women without epilepsy [16]. All these studies point out a real need for effective education on the importance of pregnancy planning and the risk of unintentional pregnancy in groups at higher risk such as WWE. A study performed in USA in 2016 demonstrated that contraceptive counselling by epileptologists and specific mention of an intrauterine device was significantly associated with patient selection of an intrauterine device as a contraceptive method, suggesting that neurologists can play an important role in patients' contraceptive choices [17].

Pregnancy counselling

The message that is delivered must be precise, careful and not alarmist. It should be recalled that there is an increased risk of fetal malformation but that it is manageable, particularly when a pregnancy has been planned, and that the accompanying measures have been taken. There is more fear of childbirth in WWE than other women [1].

The need for information is obviously felt by people with epilepsy [18]. Knowledge of WWE regarding pregnancy is lower than in women without epilepsy [19]. However, regarding pregnancy, this information is crucial [20], since, for example, unplanned pregnancies have been shown to be associated with more adverse fetal outcomes than planned pregnancies [21].

Folates

During the 1950s and 1960s, biochemical studies established that folates were essential for cellular reactions including conversion of homocysteine to methionine and DNA methylation [22]. Rapidly, in general population, maternal folate insufficiency was suspected to promote the occurrence of neural tube defect (NTD) in the offspring. NTD are one of the most common types of congenital malformations characterized by incomplete closure of the embryonic neural tube, including anencephaly and spina bifida [23]. These defects occur between 21 and 28 days after conception when most women are unaware of their pregnancies, supporting the need for folate supplementation as a preconception intervention. Indeed, in 1991, a double-blind, randomized trial provided strong evidence that folic acid prevented up to 70% of the cases in the intervention arm compared with the group that did not receive any intervention [24]. Later on, the World Health Organization (WHO) recommended a threshold at a population level, for red blood cell folate concentrations to be above 400 ng/mL (906 nmol/L), for achieving greatest reductions in NTD [25]. In 2019, the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine recommended a systematic female prepregnancy folic acid supplementation to reduce the risk of neural tube defects [26] and the Centers for Disease Control (CDC) recommend that all women of childbearing age consume 0.4 mg of folate acid per day since 1992 [27]. In WWE, two main points must be considered: i) WWE are at increased risk for having offspring with major congenital malformations (MCMs), especially NTD and ii) enzyme inducing AEDs lower serum levels of folates whereas valproate acts as a folate antagonist [28]. But unexpectively, the reduction of MCMs in the offspring of WWE who take folic acid supplement has not been demonstrated conclusively and furthermore has been questioned by the findings of the UK Epilepsy and Pregnancy Register [29]. In this study, they reported a higher rate, although non significant, of NTD in WWE having received preconceptual folic acid versus WWE who did not receive preconceptual folic acid and questioned whether the increased risk of NTD recorded in WWE could occur through mechanisms other than that of folic acid metabolism. Despite the lack of definitive evidence that folate supplementation reduces congenital malformations in the offspring of WWE, new arguments are emerging in favour of preconceptional folate acid supplementation in WWE. Emerging evidence suggests potential positive neuropsychological effects of periconceptional folate in both healthy children and children exposed in utero to AEDs [30]. Recently, the NEAD study found that

periconceptional folate was associated with higher Full Scale Intelligence Quotient at both 3 and 6 years of age in offspring of WWE [31]. In this study, the folic acid dosage ranged from 0.4 mg/day to ≥ 4 mg/day. Sample sizes were too low to explore dose-dependent effects of acid folic supplementation. It has been suggested that the dose for women taking AEDs might differ from that for the general population and that higher doses could be considered for WWE taking AEDs. Nevertheless, no definite data exist and further studies are required to determine the most effective and safe dose of folic acid in WWE. But there is actually a consensus to recommend a preconceptional and conceptional folic acid supplementation in WWE [32]. Unfortunately, recent studies still demonstrate a low prevalence of preconception folic acid use that may, once again, reflect a need for more education [28].

2-Consider seizures during pregnancy

Bidirectional influences between seizures and ongoing pregnancy should be considered and their consequences anticipated. Actually, changes in seizure frequency during pregnancy, and the effects of seizures on pregnancy and fetal development are legitimate questions. Regarding the effects of pregnancy on the frequency of seizures, two clinical situations and three possible developments could be distinguished. The two clinical situations are well-controlled as opposed to drug-resistant epilepsy. The three possible evolutions are absence of change or increase in seizure frequency, and remission (table 2). A variable that could be weighted in such changes across pregnancy is the serum concentration of the AED that could vary or be kept stable. Some drugs, especially lamotrigine [33,34] and oxcarbamazepine [35], have been shown to drop in concentration during pregnancy, up to half of previous dosage. Pregnancy increases lamotrigine clearance by more than 50% according to study calculating clearance at different time points before, during and after pregnancies in 12 subjects [36], with a similar rate (40%) of decrease from baseline contraction (outside pregnancy) for levetiracetam [37]. Noncompliance is another factor to be emphasized, since uninformed WWE could prefer discontinuing AED not to harm their offspring. In registries examining the course of seizures during pregnancy, such discontinuation of treatment are not systematically assessed, which could be a limitation [38,39].

In the case of previously well-controlled epilepsy, the most common course is no change during pregnancy. When the seizures reappear during pregnancy, they are most often due to

an increase in the metabolic catabolism of the drug, and necessitate an adjustment of the prescribed dosage [40]. The other possibility is that the worsening is consecutive to a change in the AED, made necessary by the pregnancy project (see below). A not uncommon case, for example, is the need for substituting lamotrigine for valproate for the purpose of pregnancy. In some cases, lamotrigine, even with high dosage, could not permit optimal control of the risk of seizure. Increasing further the dosage, association with a benzodiazepine can then be of help to promote the control of seizures. Ancillary measures, such as sick leave, rest, quality sleep, are often useful.

Women with epilepsy who experienced seizures in the year prior to pregnancy appear 3 to 4 times more likely to continue having seizures during pregnancy than women whose seizures are fully controlled prior to pregnancy [41]. Actually, drug-resistant epilepsies are more complicated to care, and the persistence of seizures during pregnancy should be anticipated. In a quarter of cases, an exacerbation of seizures is observed during pregnancy. This increase usually occurs during early and late pregnancy, and it is important to track down any mechanisms that may be involved. Factors that may be involved are first trimester vomiting, sleep disturbances and anxiety, and sometimes non-compliance due to fear of fetal exposure to drugs. Again, drug changes or decreased dosage may also be involved. However, a reduction of seizure frequency could be expected in WWE having catamenial epilepsy [42]. According to this study, absence of cyclical hormone variation during pregnancy benefits to WWE experiencing seizures related to the menstrual cycle: 44% of them had a more than 50% reduction in seizure frequency during their pregnancy.

The occurrence of epileptic seizures during pregnancy has an impact which depends on the type of seizure. Generalized tonic-clonic seizures could present with a risk of falls and trauma. They are associated with transient hypoxia, and a risk of SUDEP, that could have a deleterious effect of fetal heart activity [43]. Focal seizures with loss of awareness (formerly complex partial seizures) have been associated, in case reports, with fetal bradycardia [44]. Actually, loss of awareness within any type of seizure could be causal for trauma and accident [45]. Among trauma and more specifically for pregnancy, abdominal trauma has the potential to result in ruptured fetal membranes and premature labour. However, absence seizure and focal seizures with spared awareness are less harmful and could be tolerated. The balance between increased medication and impact of specific seizures should be trade off. In the EURAP study [39], among 1956 pregnancies, there were 36 status epilepticus. However, only one stillbirth or spontaneous abortion was observed close to a seizure. It is thus believed that

having seizures during pregnancy does not affect the offspring in the vast majority of cases. Actually, in a meta-analysis of 38 observational studies, Viale et al. found that women with epilepsy versus those without epilepsy had increased risks for spontaneous miscarriage, antepartum or postpartum, hypertensive disorders, induction of labour , C-section, any preterm birth and fetal growth restriction, with rather low odd-ratios varying from 1.16 to 1.67 for each complication [46]. Increased risk of being small for gestational age and preterm delivery have been associated with occurrence of seizures during pregnancy as compared to WWE without seizures during pregnancy [47]. In a retrospective study, repeated tonic-clonic seizures (at least five) during pregnancy was associated with a lower verbal IQ in 38/249 offsprings [48]. Overall death rate is 10 times more important during pregnancy among WWE as compared with women without epilepsy [49]. Major causes of death during pregnancy are SUDEP and drowning [50].

In an encouraging comparative study, it was shown that, with the expanse of more frequent AED dosage changes (in 74% of pregnant WWE as compared to 31% of non pregnant WWE during the same period), no significant differences in seizure frequency were detected between the two groups [51]. This suggests that, with a good support and careful management, pregnancy may not be a complicated period for WWE.

3-Manage the risk of fetal complications related to AED during pregnancy

It is usual to recommend exposure to the least possible drug, at the lowest possible dosage. In some cases of drug-resistant epilepsy, it is important to agree to a compromise, which can tolerate the persistence of mildly disabling seizures, which pose no risk either to mother or child.

Teratogenicity

The observation that in utero exposure to antiepileptic drugs (AED) increases the risk of congenital malformation dates back to the end of the 1960s. Both major malformations (microcephaly, growth retardation, lumbosacral spina bifida) and minor abnormalities of the face and fingers were reported. The knowledge accumulated since has made it possible to specify the nature of the AED in question. The most teratogenic treatments are valproate, phenobarbital and phenytoin [52]. Polytherapy is also more teratogenic than monotherapy.

Teratogenic and neurodevelopmental risks carried by valproate exposure during pregnancy have been well-demonstrated and have led to reconsideration of the place of this drug in the therapeutic arsenal for women with epilepsy [53]. Valproate is associated with a 10.7% risk of malformations compared to 7.1% in epileptic women and 2.3% in healthy women [54]. Compared to other ASD, valproate is more teratogenic than phenobarbital or topiramate, which are also associated with an increased risk [55]. There is a link between the dose administered and the risk of malformation, with a risk of 4.3% for doses less than 500 mg per day.

A 2016 ANSM report showed that from 2007 to 2014 the annual number of pregnancies exposed to valproic acid decreased steadily, from 2316 to 1333 (-42%). The decrease in the frequency of exposure of pregnant women to valproic acid between 2007 and 2014 was associated with an increased frequency of exposure to alternative products, including lamotrigine (1340 to 2116 annual pregnancies), levetiracetam (270 to 819), aripiprazole (323 to 823) and quetiapine (0 to 481). The pathological context of the prescription was according to the AMM indication of the drug used epilepsy in 57% of cases and bipolar disorder in 43%. The decrease in the number of pregnancies exposed to valproic acid over the period 2007-2014 was more marked for epilepsy (-56%) than for the disorder bipolar (-18%). Thus, in 2014, the proportion of bipolar disorder indication was very slightly higher than that of epilepsy (659 patients in the epilepsy indication, 679 in the bipolar disorder indication), then that in 2007 it was around 2/3 for epilepsy and 1/3 for bipolar disorder. The annual number of women of reproductive age (15-49 years) using valproic acid has decreased by at the same time, with a workforce increasing from 122,382 in 2007 to 83,712 in 2015 (data for all health insurance). In total, the drop in eight years in the number of women aged 15-49 using of valproic acid was 32%. This decrease concerned users of specialties more with MA for epilepsy (55,077 to 35,056, i.e. -36%) than those with the indication bipolar disorder (68,335 to 49,429, i.e. -28%) [56]. While there is certainly a significant fraction of these women for whom another antiepileptic treatment cannot be as effective as valproate, it is likely that some treatments have been repeated without consideration of the benefit / risk balance. Drug combinations should be avoided, especially those including topiramate or valproate [57]. However, association of levetiracetam and lamotrigine could be safe [57].

According to these data, significant changes in prescriptions for WWE have been recorded during the last decades [58]. Although a reduction in the number of child-bearing mothers

treated with VPA was measured during the period 2005-2015, no change in malformation incidence could be evidenced [59].

Neurodevelopment

Valproate

While the teratogenic effects, dominated by neural tube closure defects, of valproate have been demonstrated since the 1980s, the impact of the exposure of the fetus to valproate in utero on its subsequent psychomotor development was established only from end-2000s.

The preliminar work of Adab et al. highlighted that children exposed to VPA were at an increased risk of requiring educational support and that their verbal IQ was significantly poorer than both controls and children exposed to other AEDs [48].

Actually, starting from 2009 with the NEAD study, evidences accumulate showing that children exposed to valproate have an average IQ that is 8 to 11 points lower than children exposed to other AEDs [60, 61]. All prospective studies that made adjustment for confounding parental and child variables have shown that prenatal exposure to VPA is associated with an increased risk of poorer cognitive outcome [62]. Unfortunately, looking across the ages of assessment, it is apparent that the difficulties for the children exposed to VPA remain into the school aged year [63]. Although there is a clear dose effect, no dosage appears to be devoid of potential risk.

Older AEDs

Apart valproate, several studies have shown some old AEDs to pose a greater risk than others, including phenobarbital and phenytoin [64,65]. Concerning carbamazepine, results are more conflicting due in part to limitations in study methodologies, number of participants (small sample size), ages of children included and tools used to measure developmental outcomes [66]. Two large prospective studies that analyze factors that could confound the data have shown no significant difference in measures of cognition between carbamazepine exposed children and children exposed to other AEDs. The NEAD study found that mean IQ for children exposed to carbamazepine, lamotrigine, or phenytoin ranged from 98 to 101 with no statistical difference between drugs [61] whereas the Liverpool and Manchester Neurodevelopment Group study found that monotherapy exposure to carbamazepine or lamotrigine was not associated with impaired development [67]. Similarly, a population-based study that examined intelligence of 182 children of mothers with epilepsy and 141 control

children found that carbamazepine monotherapy with maternal serum levels within the reference range did not impair intelligence in prenatally exposed offspring [68]. But an older study points out a potential developmental delay of the in utero exposure to carbamazepine [69]. Anyway, most studies demonstrate that carbamazepine monotherapy does not seem to affect the cognition of exposed children.

Benzodiazepins

The effect of fetal exposure to benzodiazepins is largely unknown. In the general population, use of benzodiazepine for anxiety during pregnancy is associated with preterm delivery and low birth weight and potential short-term neonatal effects of hypotonia, depression, and withdrawal [70]. A methodologically sound study found no greater risk for lower language competence at ages 3 years [71]. A recent study in general population on 283 women treated antenatally by benzodiazepins provides some reassurance that neurodevelopmental effects, if present, are not likely to be of great magnitude in children exposed to benzodiazepines and hypnotics in utero [72] . Unfortunately, data are lacking in WWE offspring.

Newer AEDs

There is very limited high-quality data on newer medications, but the preponderance of the evidence suggests that lamotrigine and levetiracetam have no significant neurodevelopmental adverse effects.

Lamotrigine

Lamotrigine safety has ever been addressed by the NEAD study (see below). Additional sub-investigations within the NEAD study have shown that lamotrigine appears to be better than valproate and carbamazepine with regards to motor development, and better than valproate and phenytoin with regards to adaptive and emotional / behavioral functioning [73,74]. A study published by the Liverpool and Manchester Neurodevelopment Group showed no significant increase in the risk of neurodevelopmental disorders in children exposed to monotherapy with lamotrigine [75]. In a population-based case–cohort study using Danish nationwide register data from 2005 to 2008 that included 636 cases and 434 controls, learning disabilities were identified among 7.1% cases compared with 3.7% for controls. Among cases not exposed to polytherapy (n=556), in utero exposure to lamotrigine compared with another antiepileptic drug was associated with the lowest adjusted risk (OR 0.42) [76].

Levetiracetam

A study on two small prospective cohorts in United Kingdom found that children exposed to levetiracetam in utero were not at an increased risk of delayed early cognitive development under the age of 24 months [77]. The follow up study evaluating these children at age 36 to 54 months showed that they did not differ from unexposed controls on any scale administered [78].

Topiramate

While topiramate is known to affect cognition, especially verbal domains [79], during active use, there is insufficient evidence to determine whether there is any neurodevelop-mental effect. We only found one cross-sectional observational study that compared children exposed to monotherapy levetiracetam (n = 42), topiramate (n = 27), or valproate (n = 47) [75]. In this study, topiramate was not found to be associated with reductions in child cognitive abilities, even with high doses.

Other new AEDs

Whether in utero exposure to other new AEDs affects cognitive neurodevelopment is yet to be determined.

Polytherapy

In all studies, polytherapy is associated with a lesser cognitive outcome [80, 81]. A 2014 Cochrane review including 28 studies concluded that AED polytherapy led to poorer developmental outcomes and IQ compared with healthy controls, epileptic controls and unspecified monotherapy [82]. However, most studies predominately involved older AEDs, so the risk of polytherapy comprised of the newer AEDs is not clear [83].

Other factors

In assessing cognitive outcomes of AED exposure, there are a myriad of potential confounding factors including maternal IQ, type and severity of maternal epilepsy, polytherapy, socioeconomic status, presence of other comorbidities, and breastfeeding exposure [84].

Concerning maternal epilepsy, there is an increased risk of neurodevelopmental disorders in pregnant women whose epilepsy is not optimally controlled, especially if the repeated seizures are generalized tonic-clonic [70].

Autism and behavioral outcome

Valproate

Specific behavioral disorders, such as attention deficit hyperactivity disorder, autism and autism spectrum disorders, also appear to be associated with in utero exposure to valproate [85].

A population-based study of all children born alive in Denmark from 1996 to 2006 demonstrated that, among 655 615 children, the 508 children exposed to valproate had an absolute risk of 4.42% for autism spectrum and an absolute risk of 2.50% for childhood autism. The increased risk compared to controls was of 5 for autism spectrum disorder and 2.5 for autism [86]. As for neurodevelopmental delay, a dose effect was suspected in further studies [87].
A recent study on the same Danish National Prescription Registry has demonstrated that maternal use of valproate, but not other AEDs, during pregnancy was associated with an increased risk of attention-deficit/hyperactivity disorder in the offspring [88].

Benzodiazepines

Several studies in general population suggest that in utero exposure to benzodiazepines is not associated to significant behavioural symptoms [72]. Associations between prenatal benzodiazepine exposure and gross motor and fine motor impairment have been observed in toddlers, although the gross motor delay resolved as children grew older [89].

Other AEDs

A recent systematic review and network meta-analysis found that, as expected, Valproate alone or combined with another AED is associated with the greatest odds of adverse neurodevelopmental and autistic outcomes compared with control [90]. Unexpectively, they also found that oxcarbazepine and lamotrigine were associated with increased occurrence of

autism/dyspraxia. An alert with these two drugs had never been published before. Of course, these results are a major matter of concern but two major biases must be noted:

1) The heterogeneity of the maternal population and of the methology of the studies: this meta-analysis explored 29 cohort studies (5100 patients) published between 1989 and 2016 but the network meta-analysis (NMA) concerned only 5 cohort studies for the autism/dyspraxia section. 2551 children exposed in utero with 12 treatments were analyzed. Treatments consisted in various combinations of lamotrigine, valproate, carbamazepine, levetiracetam, oxcarbazepine, clonazepam, and phenytoin. This 5 cohort studies included both offspring of WWE and women with psychiatric disorders. Restricting the NMA to studies including only WWE as their treatment indication excluded oxcarbazepine from the significant results and controlling results accorded to the adequacy of follow-up of cohorts excluded lamotrigine
2) The authors selected as primary outcome autism/dyspraxia without distinction between these two distinct behavioural disorders with very different outcomes

To note, Rasalam et al. [91] also reported an increased risk of autistic spectrum diagnosis in children exposed to carbamazepine, however, this has not been replicated by others studies [92], including the large population study based on the Danish register [86].

These conflicting results argue for long-term follow-up studies to further delineate neurodevelopmental risks in children exposed in utero to AEDs. Nevertheless, all studies converge to demonstrate that Valproate is significantly associated with more children experiencing autism, dyspraxia, language, cognitive and psychomotor developmental delays.

4. Anticipate delivery and breastfeeding

Delivery

Anticipation of the course of childbirth is a frequent concern for pregnant women. In the case of WWE, there is the additional fear that a seizure may interfere with childbirth. Moreover, this fear could be shared by the obstetrician who may favor a planned cesarean delivery to limit this risk. Accordingly Caesarean-section (C-section) has been reported more frequently in WWE than those without [93-95], and increase in proportions of induced labour ($p<0.005$) and use of epidural analgesia ($p<0.005$) have been observed [96]. Preterm delivery is reported

more frequently in WWE (OR 2.83, 95%CI 1.03-7.76) [95]. Despite the fact that there is a global trend, including women without epilepsy, showing an increase in C-section rate and induction of labour, such a systematic approach for WWE has some limitations. In 45 out of 67 C-section performed in 103 WWE (66.7% as compared to 24.9% in the control group), the relevant indication included epilepsy, meaning that obstetrical reasons for C-section were less prevalent [95]. A similar reason explained high rate of C-section in Australian WWE [97] and in Norway [98]. Given that, a C-section, in particular acute, is associated with an increased health-related risk to both mother and child, the advantage-risk ratio should be balanced for each case. Actually, seizure is a rare event that may complicate childbirth. Seizure has been reported in only 2% of WWE (with slight variations depending on which AED they are) during delivery [99], meaning that in the exceeding large proportion of delivery no seizures are observed.

Breastfeeding

Breastfeeding is worldwide encouraged, since it is associated with a lower risk of infections and a decrease in mortality in infants [100]. These benefits include mothers, who experienced less risk of postpartum depression and cardiovascular disease. Exclusive breastfeeding has been recommended by the American Academy of Pediatrics for the first six months of live, although economic constraints could lead women to interrupt or manage breastfeeding to go back to work before this time point. Regarding WWE, presence of AED in the maternal milk is a major cause of concerns, although the balance between benefits and risks is rarely discussed. In the mind of care givers and mothers, the fear of adverse effects (sedation, liver dysfunction, cutaneous rash) due to AED in breastfeed infants overcomes the expected benefits. Among benefits, higher IQ showed after breastfeeding from women without epilepsy as compared to formula-fed infants [100] has also been demonstrated for WWE [101]. In a distinct study from Norway, the same results were observed, with infants exposed to AED during pregnancy and breastfeeding had better neurodevelopmental outcomes at 18 months than those without breastfeeding [102].

Levels of exposure to breastfed infants are related to AED use. Administration of phenobarbitone, ethosuximide, and primidone to lactating WWE expose to a level of exposure to infants estimated at 100%, 50% and >10% of the weight-adjusted therapeutic dose [103]. Despite exposure to breastfeeding has been shown to be beneficial for offsprings of WWE, a smaller rate is observed as compared to women without epilepsy [104].

However, we must keep in mind that the precautionary principle may advocate the avoidance of breastfeeding in the case of polytherapy or therapy including sedative molecules.

5. CONCLUSION

For WWE, the reproductive choice is complex. Women need accurate information tailored to their individual circumstances in order to make informed decisions about their families. Counselling is advised concerning teratogenic and developmental risks associated to the prescription of AEDs. AEDs modifications must always be balanced against the need for seizure control. In all circumstances, clinician must have knowledge of literature to enable appropriate decision and counselling.

Tables

Table 1: Interactions between hormonal contraceptives and antiepileptic drugs

	COC	P-oP	P-oI	IUD	P-oIUD
classical enzyme-inducers AEDs					
phenobarbitone	no	no	no	yes	yes
phenytoin	no	no	no	yes	yes
carbamazepine	no	no	no	yes	yes
oxcarbazepine	no	no	no	yes	yes
eslicarbazepine	no	no	no	yes	yes
dose-dependent enzyme inducers					
topiramate > 200 mg/day	no	no	no	yes	yes
perampanel at 12 mg/day	no	no	no	yes	yes
enzyme-inducer AED for hormonal contraception					
felbamate	no	no	no	yes	yes
rufinamide	no	no	no	yes	yes
enzyme-inhibitor AED					
sodium valproate	yes	yes	yes	yes	yes
neutral AEDs					
brivaracetam	yes	yes	yes	yes	yes
gabapentin	yes	yes	yes	yes	yes
lacosamide	yes	yes	yes	yes	yes
lamotrigine	yes	yes	yes	yes	yes
levetiracetam,	yes	yes	yes	yes	yes
perampanel ≤ 10 mg/day	yes	yes	yes	yes	yes
pregabaline	yes	yes	yes	yes	yes
zonisamide	yes	yes	yes	yes	yes

AEDs= antiepileptic drugs, Combined oral contraceptive (COC), Progestin-only pills (P-oP) , Progestin-only implants (P-oI) , intrauterine device (IUD), Progestin-only intrauterine device (P-oIUD)

Table 2: Effect of pregnancy on epilepsy

Pregnancy effect on seizure frequency	**No change**	**Increase**	**Decrease**
Well-controlled epilepsy	Often	Occasional (consider change in AED, decreased dosage)	Not applicable
Drug-resistant epilepsy	50%	25% (consider change in AED, decreased dosage, vomiting, sleep disturbances, anxiety, lack of compliance)	25%

References

[1] Turner K, Piazini A, Franza A, Canger R, Canevini M, Marconi A. Do women with epilepsy have more fear of childbirth during pregnancy compared with women without epilepsy? A case-control study. Birth 2008;35:147‐52. doi: 10.1111/j.1523-536X.2008.00228.x.

[2] Reimers A, Brodtkorb E, Sabers A. Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations. Seizure 2015;28:66–70. DOI: 10.1016/j.seizure.2015.03.006

[3] Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. Epilepsia 1997;38:317–23. DOI: 10.1111/j.1528-1157.1997.tb01123.x

[4] Fycompa prescribing information. U.S. Food and Drug Administration; 2014, http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202834lbl.pdf.

[5] Palmer KJ, McTavish D. Felbamate. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in epilepsy. Drugs 1993;45(6):1041-1065. DOI: 10.2165/00003495-199345060-00008

[6] Saano V, Glue P, Banfield CR, Reidenberg P, Colucci RD, Meehan JW, et al. Effects of felbamate on the pharmacokinetics of a low-dose combination oral contraceptive. Clin Pharmacol Ther 1995;58:523–31. DOI: 10.1016/0009-9236(95)90172-8

[7] Perucca E, Cloyd J, Critchley D, Fuseau E. Rufinamide: clinical pharmacokinetics and concentration-response relationships in patients with epilepsy. Epilepsia 2008;49(7):1123-41. DOI: 10.1111/j.1528-1167.2008.01665.x

[8] Sales Vieira C, Pack, Roberts K, Davis AR. A pilot study of levonorgestrel concentrations and bleeding patterns in women with epilepsy using a levonorgestrel IUD and treated with antiepileptic drugs. Contraception 2019;99:251–255.
DOI: 10.1016/j.contraception.2018.11.018

[9] Herzog AG, Mandle HB, Cahill KE, Fowler KM, Hauser WA. Predictors of unintended pregnancy in women with epilepsy. Neurology 2017;88:728–733.
DOI: 10.1212/WNL.0000000000003637

[10] Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res 2001;47:151–4. DOI: 10.1016/s0920-1211(01)00305-9

[11] Herzog AG, Blum AS, Farina EL, Maestri XE, Newman J, Garcia E, et al. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. Neurology 2009;72:911–4. DOI: 10.1212/01.wnl.0000344167.78102.f0

[12] Galimberti CA, Mazzucchelli I, Arbasino C, Canevini MP, Fattore C, Perucca E. Increased apparent oral clearance of valproic acid during intake of com- bined contraceptive steroids in women with epilepsy. Epilepsia 2006;47: 1569–72. DOI: 10.1111/j.1528-1167.2006.00629.x

[13] Rauchenzauner M, Deichmann S, Pittschieler S, Bergmann M,PrieschlM, Unterberger I, et al. Bidirectional interaction between oral contraception and lamotrigine in women with epilepsy – Role of progestins Seizure: 74 (2020) 89–92. DOI: 10.1016/j.seizure.2019.11.011

[14] Fairgrieve SD, Jackson M, Jonas P, Walshaw D, White K, Montgomery TL, Burn J, Lynch SA .Population based, prospective study of the care of womenwith epilepsy in pregnancy BMJ 2000;321: 674-675. DOI: 10.1136/bmj.321.7262.674

[15] Pack AM, Davis AR, Kritzer J, Yoon A, Camus. A Antiepileptic drugs: Are women aware of interactions with oral contraceptives and potential teratogenicity? Epilepsy & Behavior 2009;14:640–644. DOI: 10.1016/j.yebeh.2009.01.024

[16] Johnson EL, Burke AE, Wang A, Pennell PB. Unintended pregnancy, prenatal care, newborn outcomes, and breastfeeding in women with epilepsy. Neurology 2018;91:e1031-e1039. DOI: 10.1212/WNL.0000000000006173

[17] Espinera AR, Gavvala J , Bellinski I, Kennedy J, Macken MP, Narechania A, et al. Counseling by epileptologists affects contraceptive choices of women with epilepsy. Epilepsy & Behavior 2016;65: 1–6. DOI: 10.1016/j.yebeh.2016.08.021

[18] Henning O, Alfstad KA, Nakken KO, Lossius MI. A call for better information about epilepsy: The patients' perspective—An online survey. Seizure 2019;69:173‑9. DOI: 10.1016/j.seizure.2019.04.015

[19] Saramma PP, Sarma PS, Thomas SV. Women with epilepsy have poorer knowledge and skills in child rearing than women without epilepsy. Seizure 2011;20(7):575‑9. DOI: 10.1016/j.seizure.2011.04.008

[20] Leach JP, Smith PE, Craig J, Bagary M, Cavanagh D, Duncan S, et al. Epilepsy and Pregnancy: For healthy pregnancies and happy outcomes. Suggestions for service improvements from the Multispecialty UK Epilepsy Mortality Group. Seizure 2017;50:67‑72. DOI: 10.1016/j.seizure.2017.05.004

[21] Zhang Y, Song C, Wang X, Jiang Y, Zhao J, Yuan F, et al. Clinical characteristics and fetal outcomes in women with epilepsy with planned and unplanned pregnancy: A retrospective study. Seizure 2020;79:97‑102.DOI: 10.1016/j.seizure.2020.05.011

[22] Kancherla V, Black RE. Historical perspective on folic acid and challenges in estimating global prevalence of neural tube defects Ann. N.Y. Acad. Sci. 2018;1414:20–30. DOI: 10.1111/nyas.13601

[23] Parker, S.E., M.M. Yazdy, A.A. Mitchell, *et al*. A description of spina bifida cases and co-occurring malformations, 1976–2011. *Am. J. Med. Genet. A* 2014; 164A: 432–440. DOI: 10.1002/ajmg.a.36324

[24] MRC Vitamin Study Research Group. Prevention of neural tube defects: results of theMedical Research Council Vitamin Study. Lancet 1991; 338: 131–137.

[25] Cordero, A.M., K.S. Crider, L.M. Rogers, et al. Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects: World Health Organization guidelines. MMWRMorb.Mortal.Wkly. Rep. 2015;64: 421–423.

[26] ACOG Committee Opinion No. 762: Prepregnancy Counseling Obstet Gynecol 2019;133(1):e78-e89.

[27] CDC. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR 1992;41(RR-14):1–7.

[28] Herzog AG, MacEachern DB, Mandle HB, Cahill KE, Fowler KM, Davis AR, Allen Hauser W. Folic acid use by women with epilepsy: Findings of the Epilepsy Birth Control Registry. Epilepsy Behav.2017;72:156-160. DOI: 10.1016/j.yebeh.2017.05.007

[29] Morrow JI, Hunt SJ, Russell AJ, Smithson WH, Parsons L, Robertson I, et al. Folic acid use and major congenital malformations in offspring of womenwith epilepsy: a prospective study fromthe UK epilepsy and pregnancy register. J Neurol Neurosurg Psychiatry 2009;80(5):506–11. DOI: 10.1136/jnnp.2008.156109

[30] 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;23:199–206. DOI: 10.1111/j.1365-3016.2009.01032.x

[31] Meador KJ, Pennell PB, May RC, Brown CA, Baker G, Bromley R, Loring DW, Cohen MJ; NEAD Investigator Group. Effects of periconceptional folate on cognition in children of women with epilepsy: NEAD study. Neurology 2020;94(7):e729-e740. DOI: 10.1212/WNL.0000000000008757

[32] Keni RR, Jose M, A.S. R, Baishya J, Sankara Sarma P, Thomas SV. Anti-epileptic drug and folic acid usage during pregnancy, seizure and malformation outcomes: Changes over two decades in the Kerala Registry of Epilepsy and Pregnancy. Epilepsy Research 2020;159:106250. DOI: 10.1016/j.eplepsyres.2019.106250

[33] de Haan GJ, Edelbroek P, Segers J, Engelsman M, Lindhout D, Dévilé-Notschaele M, et al. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. Neurology 2004;63(3):571-3. doi: 10.1212/01.wnl.0000133213.10244.fd.

[34] Pennell PB, Newport DJ, Stowe ZN, Helmers SL, Montgomery JQ, Henry TR. The impact of pregnancy and childbirth on the metabolism of lamotrigine. Neurology 2004;62(2):292-5. doi: 10.1212/01.wnl.0000103286.47129.f8. Erratum in: Neurology. 2010;74(24):2028.

[35] Christensen J, Sabers A, Sidenius P. Oxcarbazepine concentrations during pregnancy: a retrospective study in patients with epilepsy. Neurology 2006;67(8):1497-9. doi: 10.1212/01.wnl.0000240047.11166.0e.

[36] Tran TA, Leppik IE, Blesi K, Sathanandan ST, Remmel R. Lamotrigine clearance during pregnancy. Neurology 2002;59(2):251-5. doi: 10.1212/wnl.59.2.251.

[37] Tomson T, Palm R, Källén K, Ben-Menachem E, Söderfeldt B, Danielsson B, et al. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. Epilepsia 2007;48(6):1111-6. doi: 10.1111/j.1528-1167.2007.01032.x.

[38] 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. doi: 10.1111/j.1528-1167.2007.01412.x. Epub 2007 Nov 21.

[39] EURAP Study Group. Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. Neurology 2006;66(3):354-60. doi: 10.1212/01.wnl.0000195888.51845.80.

[40] 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. doi: 10.1016/j.yebeh.2013.06.026.

[41] Vajda FJE, O'Brien TJ, Graham JE, Hitchcock AA, Lander CM, Eadie MJ. Predicting epileptic seizure control during pregnancy. Epilepsy Behav 2018;78:91-95. doi: 10.1016/j.yebeh.2017.10.017.

[42] Cagnetti C, Lattanzi S, Foschi N, Provinciali L, Silvestrini M. Seizure course during pregnancy in catamenial epilepsy. Neurology 2014;83(4):339-44. doi: 10.1212/WNL.0000000000000619.

[43] Teramo K, Hiilesmaa V, Bardy A, Saarikoski S. Fetal heart rate during a maternal grand mal epileptic seizure. J Perinat Med 1979;7(1):3-6. doi: 10.1515/jpme.1979.7.1.3.

[44] Sahoo S, Klein P. Maternal complex partial seizure associated with fetal distress. Arch Neurol 2005;62(8):1304-5. doi: 10.1001/archneur.62.8.1304.

[45] Tinker SC, Reefhuis J, Dellinger AM, Jamieson DJ; National Birth Defects Prevention Study. Epidemiology of maternal injuries during pregnancy in a population-based study, 1997-2005. J Womens Health (Larchmt) 2010;19(12):2211-8. doi: 10.1089/jwh.2010.2160.

[46] Viale L, Allotey J, Cheong-See F, Arroyo-Manzano D, Mccorry D, Bagary M, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 2015;386(10006):1845-52. doi: 10.1016/S0140-6736(15)00045-8.

[47] 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. doi: 10.1001/archneurol.2009.142..

[48] Adab N, Kini U, Vinten J, Ayres J, Baker G, Clayton-Smith J, et al. The longer term outcome of children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry 2004;75(11):1575-83. doi: 10.1136/jnnp.2003.029132.

[49] Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia 2014;55(7):e72-4. doi: 10.1111/epi.12621.

[50] Kinney MO, Morrow J. Epilepsy in pregnancy. BMJ 2016;353:i2880. doi: 10.1136/bmj.i2880.

[51] Pennell PB, French JA, May RC, Gerard E, Kalayjian L, Penovich P, et al. Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy. N Engl J Med 2020;383(26):2547-2556. doi: 10.1056/NEJMoa2008663.

[52] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10(7):609-17. doi: 10.1016/S1474-4422(11)70107-7.

[53] 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):210-218. doi: 10.1016/S1474-4422(15)00314-2.

[54] Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008;81(1):1-13. doi: 10.1016/j.eplepsyres.2008.04.022.

[55] Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Lancet Neurol 2012;11(9):803-13. doi: 10.1016/S1474-4422(12)70103-5.

[56] https://www.amisp.fr/site/documents-liens/send/8-journees-annuelles-2019/201-6-1-exposition-a-l-acide-valproique-et-ses-derives-au-cours-de-la-grossesse-en-france-de-2007-a-2014-une-etude-observationnelle-sur-les-donnees-du-sniiram

[57] Vajda FJE, O'Brien TJ, Graham JE, Hitchcock AA, Lander CM, Eadie MJ. Antiepileptic drug polytherapy in pregnant women with epilepsy. Acta Neurol Scand 2018;138(2):115-121. doi: 10.1111/ane.12965.

[58] Meador KJ, Pennell PB, May RC, Gerard E, Kalayjian L, Velez-Ruiz N, et al. Changes in antiepileptic drug-prescribing patterns in pregnant women with epilepsy. Epilepsy Behav 2018;84:10-14. doi: 10.1016/j.yebeh.2018.04.009.

[59] Shihman B, Goldstein L, Amiel N, Benninger F. Antiepileptic drug treatment during pregnancy and delivery in women with epilepsy-A retrospective single center study. Epilepsy Res 2019;149:66-69. doi: 10.1016/j.eplepsyres.2018.11.010.

[60] Meador KJ, Penovich P, Baker GA, Pennell PB, Bromfield E, Pack A, et al. Antiepileptic drug use in women of childbearing age. Epilepsy Behav 2009;15(3):339-43. doi: 10.1016/j.yebeh.2009.04.026.

[61] Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell D, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM. 2009;360:1597–605. DOI: 10.1056/NEJMoa0803531

[62] McCorry D, Bromley R. Does in utero exposure of antiepileptic drugs lead to failure to reach full cognitive potential? Seizure 2015;28:51-6. doi: 10.1016/j.seizure.2015.01.019.

[63] Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, 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. doi: 10.1016/S1474-4422(12)70323-X.

[64] Reinisch JM, Sanders SA, Mortensen EL, Rubin DB. In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA. 1995;274:1518–25.

[65] Hanson JW, Myrianthopoulos NC, Harvey MA, Smith DW. Risks to offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. J Pediatr 1976;89:662–8. doi: 10.1016/s0022-3476(76)80414-3.

[66] Nicolai J, Vles JSH, Aldenkamp AP. Neurodevelopmental delay in children exposed to antiepileptic drugs in utero: a critical review directed at structural study-bias. J Neurol Sci 2008;271:1–14. doi: 10.1016/j.jns.2008.03.004.

[67] Bromley RL, Mawer G, Love J, et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010;51:2058–65 DOI: 10.1111/j.1528-1167.2010.02668.x

[68] Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M, Matila R, Kotila M, et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology 2004;62(1):28-32. DOI: 10.1212/wnl.62.1.28

[69] 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. DOI: 10.1136/adc.2009.176990

[70] Shyken JM, Babbar S, Babbar S, Forinash A Benzodiazepines in Pregnancy. Clin Obstet Gynecol 2019;62(1):156-167. DOI: 10.1097/GRF.0000000000000417

[71] Odsbu I, Skurtveit S, Selmer R, Roth C, Hernandez-Diaz S, Handal M. Prenatal exposure to anxiolytics and hypnotics and language competence at 3 years of age. Eur J Clin Pharmacol 2015;71(3):283-91. doi: 10.1007/s00228-014-1797-4

[72] Lupattelli A, Chambers CD, Bandoli G, Handal M, Skurtveit S, Nordeng H. Association of Maternal Use of Benzodiazepines and Z-Hypnotics During Pregnancy With Motor and Communication Skills and Attention-Deficit/Hyperactivity Disorder Symptoms in Preschoolers. JAMA Netw Open 2019;2(4):e191435. doi: 10.1001/jamanetworkopen.2019.1435.

[73] Cohen MJ, Meador KJ, Browning N, Baker GA, Clayton-Smith J, Kalayjian LA et al. Fetal antiepileptic drug exposure: motor, adaptive, and emotional/behavioral functioning at age 3 years. Epilepsy Behav 2011; 22(2):240–246. DOI: 10.1016/j.yebeh.2011.06.014

[74] Cohen MJ, Meador KJ, Browning N, May R, Baker GA, Clayton-Smith et al. Fetal antiepileptic drug exposure: adaptive and emotional/behavioral functioning at age 6 years. Epilepsy Behav 2013; 29(2):308–315 DOI: 10.1016/j.yebeh.2013.08.001

[75] Bromley RL, Calderbank R, Cheyne CP, Rooney C, Trayner P, Clayton-Smith J, et al. Cognition in school-age children exposed to levetiracetam, topiramate, or sodium valproate. Neurology 2016;87(18):1943-1953 DOI: 10.1212/WNL.0000000000003157

[76] Bech LF, Polcwiartek C, Kragholm K, Andersen MP, Rohde C, Torp-Pedersen C, et al. In utero exposure to antiepileptic drugs is associated with learning disabilities among offspring. J Neurol Neurosurg Psychiatry 2018;89(12):1324-1331 DOI: 10.1136/jnnp-2018-318386

[77] 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): 383–389. DOI: 10.1212/WNL.0b013e3182088297

[78] Shallcross R, Bromley RL, Cheyne CP, García-Fiñana M, Irwin B, Morrow J, et al. In utero exposure to levetiracetam vs. valproate: development and language at 3 years of age. Neurology 2014; 82(3):213–221. DOI: 10.1212/WNL.0000000000000030

[79] Witt JA, Helmstaedter C. Monitoring the cognitive effects of antiepileptic pharmacotherapy--approaching the individual patient.Epilepsy Behav 2013;26(3):450-6. DOI: 10.1016/j.yebeh.2012.09.015

[80] Koch S, Titze K, Zimmermann RB, Schröder M, Lehmkuhl U, Rauh H. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia 1999;40(9):1237–1243. DOI: 10.1111/j.1528-1157.1999.tb00852.x

[81] Losche G, Steinhausen HC, Koch S, Helge H. The psychological development of children of epileptic parents. II. The differential impact of intrauterine exposure to anticonvulsant drugs and further influential factors. Acta Paediatr 1994; 83(9):961–966. DOI: 10.1111/j.1651-2227.1994.tb13181.x

[82] Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev 2014;10:Cd010236. DOI: 10.1002/14651858.

[83] Velez-Ruiz NJ, Meador KJ. Neurodevelopmental effects of fetal antiepileptic drug exposure.Drug Saf 2015;38(3):271-8. DOI: 10.1007/s40264-015-0269-9

[84] Kellogg M, Meador K Neurodevelopmental Effects of Antiepileptic Drugs. J.Neurochem Res 2017;42(7):2065-2070. DOI: 10.1007/s11064-017-2262-4

[85] Meador KJ, Loring DW. Developmental effects of antiepileptic drugs and the need for improved regulations. Neurology 2016; 86: 297-306.DOI: 10.1212/WNL.0000000000002119

[86] Christensen J, Koops Grønborg T, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013;309(16):1696-703. doi: 10.1001/jama.2013.2270.

[87] Wood AG, Nadebaum C Anderson V, Reutens D, Barton S, O'Brien TJ, et al. Prospective assessment of autism traits in children exposed to antiepileptic drugs during pregnancy Epilepsia 56(7):1047–1055, 2015. DOI: 10.1111/epi.13007

[88] Christensen J, Pedersen L, 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. doi: 10.1001/jamanetworkopen.2018.6606

[89] Mortensen JT, Olsen J, Larsen H, Bendsen J, Obel C, Sørensen HT. Psychomotor development in children exposed in utero to benzodiazepines, antidepressants, neuroleptics, and anti-epileptics. Eur J Epidemiol 2003;18(8):769-71. doi: 10.1023/a:1025306304635.

[90] Veroniki AA, Rios P, Cogo E, Straus SE, Finkelstein Y, Kealey R, et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open 2017;7(7):e017248. doi: 10.1136/bmjopen-2017-017248

[91] Rasalam AD, Hailey H, William JHG, Moore SJ, Turnpenny PD, Lloyd DJ, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 2005;47(8):551-5. doi: 10.1017/s0012162205001076.

[92] Bromley RL, Mawer GE, Briggs M, Cheyne C, Clayton-Smith J, García-Fiñana M et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. J Neurol Neurosurg Psychiatry 2013;84(6):637-43. doi: 10.1136/jnnp-2012-304270.

[93] Vajda FJ, O'Brien TJ, Graham J, Lander CM, Eadie MJ. The outcomes of pregnancy in women with untreated epilepsy. Seizure 2015;24:77-81. doi: 10.1016/j.seizure.2014.08.008.

[94] Allotey J, Aroyo-Manzano D, Lopez P, Viale L, Zamora J, Thangaratinam S. Global variation in pregnancy complications in women with epilepsy: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2017;215:12-19. doi: 10.1016/j.ejogrb.2017.05.016.

[95] Melikova S, Bagirova H, Magalov S. The impact of maternal epilepsy on delivery and neonatal outcomes. Childs Nerv Syst. 2020;36(4):775-782. doi: 10.1007/s00381-019-04435-2.

[96] Danielsson KC, Gilhus NE, Borthen I, Lie RT, Morken NH. Maternal complications in pregnancy and childbirth for women with epilepsy: Time trends in a nationwide cohort. PLoS One 2019;14(11):e0225334. doi: 10.1371/journal.pone.0225334.

[97] Vajda FJE, O'Brien TJ, Graham JE, Hitchcock AA, Kuhn RJP, Lander CM, et al. Cesarean section in Australian women with epilepsy. Epilepsy Behav 2018;89:126-129. doi: 10.1016/j.yebeh.2018.10.008.

[98] Farmen AH, Grundt JH, Nakling JO, Mowinckel P, Nakken KO, Lossius MI. Increased rate of acute caesarean sections in women with epilepsy: results from the Oppland Perinatal Database in Norway. Eur J Neurol. 2019;26(4):617-623. doi: 10.1111/ene.13865.

[99] Sveberg L, Svalheim S, Taubøll E. The impact of seizures on pregnancy and delivery. Seizure 2015;28:35-8. doi: 10.1016/j.seizure.2015.02.020.

[100] Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, et al. Breastfeeding and the use of human milk. Pediatrics 2005;115(2):496-506. doi: 10.1542/peds.2004-2491.

[101] Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. JAMA Pediatr 2014;168(8):729-36. doi: 10.1001/jamapediatrics.2014.118.

[102] 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 2013;70(11):1367-74. doi: 10.1001/jamaneurol.2013.4290.

[103] Ito S. Drug therapy for breast-feeding women. N Engl J Med. 2000 Jul 13;343(2):118-26. doi: 10.1056/NEJM200007133430208. Erratum in: N Engl J Med 2000 Nov 2;343(18):1348.

[104] Johnson EL, Burke AE, Wang A, Pennell PB. Unintended pregnancy, prenatal care, newborn outcomes, and breastfeeding in women with epilepsy. Neurology 2018;91(11):e1031-e1039. doi: 10.1212/WNL.0000000000006173.