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Review

Treatment and care of women with epilepsy before, during, and after pregnancy: a practical guide

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***Abstract*:** Women with epilepsy (WWE) wishing for a child represent a highly relevant subgroup of epilepsy patients. The treating epileptologist needs to delineate the epilepsy syndrome and choose the appropriate anti-seizure medication (ASM) considering the main goal of seizure freedom, teratogenic risks, changes in drug metabolism during pregnancy and postpartum, demanding for up-titration during and down-titration after pregnancy. Folic acid or vitamin K supplements and breastfeeding are also discussed in this review. Lamotrigine and levetiracetam have the lowest teratogenic potential. Data on teratogenic risks are also favorable for oxcarbazepine, whereas topiramate tends to have an unfavorable profile. Valproate needs special emphasis. It is most effective in generalized seizures but should be avoided whenever possible due to its teratogenic effects and the negative impact on neuropsychological development of *in utero*-exposed children. Valproate still has its justification in patients not achieving seizure freedom with other ASMs or if a woman decides to or cannot become pregnant for any reason. When valproate is the most appropriate treatment option, the patient and caregiver must be fully informed of the risks associated with its use during pregnancies. Folate supplementation is recommended to reduce the risk of major congenital malformations. However, there is insufficient information to address the optimal dose and it is unclear whether higher doses offer greater protection. There is currently no general recommendation for a peripartum vitamin K prophylaxis. During pregnancy most ASMs (e.g. lamotrigine, oxcarbazepine, and levetiracetam) need to be increased to compensate for the decline in serum levels; exceptions are valproate and carbamazepine. Postpartum, baseline levels are reached relatively fast, and down-titration is performed empirically. Many ASMs in monotherapy are (moderately) safe for breastfeeding and women should be encouraged to do so. This review provides a practically oriented overview of the complex management of WWE before, during, and after pregnancy.

Keywords: anti-seizure medicine, breast feeding, folate, major congenital malformation, teratogenicity

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Introduction

With approximately 15 million patients worldwide, women with epilepsy of childbearing age (WWE) represent a relevant subgroup of epilepsy patients.[1] Their special needs are manifold and encompass contraception, the wish to have children, folic acid supplementation, teratogenic risks, and seizure control during pregnancy, changes of anti-seizure medication's (ASM) serum levels during pregnancy and their adjustment during pregnancy and postpartum, birth mode, puerperium, and breast feeding. The epileptologist should consider these issues together with the underlying epilepsy syndrome and choose the appropriate ASM after thorough counseling with the patient.

This comprehensive narrative review aims to cover the topics of counseling before, during, and

after pregnancy, serving as a practical guide informing clinicians. The topic of contraception is beyond the scope of this article and can be read elsewhere.[2]

Planning for pregnancy

Adequate seizure control without unacceptable adverse events for the child is the main goal of epilepsy treatment. Tonic-clonic seizures have the highest risk for sudden unexpecetd death in epilepsy (SUDEP) and seizure-related injuries.[3] During pregnancy, they may lead to maternal hypoxia, lactic acidosis, and fetal asphyxia.[4] It is therefore advisable to measure preconceptional ASM levels (before morning dose), using them as a reference to guide dose adjustments during a future pregnancy. Preconceptional education about these pharmacological issues with the consequent need for increasing the dose of ASMs during pregnancy might improve adherence with improved seizure control.

Preconceptional counseling should ensure that the ASM with the lowest teratogenic risk for a given epilepsy syndrome is used in the lowest effective dose. Monotherapies generally bear a lower risk than polytherapy.[5] However, the type of ASM chosen in polytherapy is more important than the number of ASM prescribed.[6] In particular, valproate is not only associated with a higher teratogenic risk in monotherapy but is also the main factor for adverse outcomes of pregnancies in polytherapy[7–10] including the negative impact on the neurocognitive outcome of the offspring.[11–13]

Hormonal disturbances

Valproate is associated with increased testosterone levels, weight gain, polycystic ovary syndrome, and non-alcoholic fatty liver disease.[14] Furthermore, it increases the expression of the sexual hormone-binding protein (SHBG), leading to lower estrogen levels. Enzyme-inducing ASMs (phenobarbital, phenytoin, carbamazepine) can be associated with reduced fertility and menstrual disturbances.[15]

Besides adverse effects of ASMs, epilepsy can be associated with reproductive dysfunction due to polycystic ovary syndrome, hypothalamic amenorrhea, premature ovarian failure, and functional hyperprolactinemia leading to anovulatory cycles.[14] In contrast to ovulatory cycles, the risk for tonic-clonic seizures increases up to threefold, seizures in general up to 1.5-fold.[14] The lack of progesterone elevation is supposed causative. In temporal lobe epilepsy, the limbic system impacts the hypothalamic–pituitary axis even in the interictal phases.[14] Postictal hyperprolactinemia occurs after focal to tonic-clonic seizures (88%), after focal impaired awareness seizures (78%), and focal aware seizures (22%) arising from the temporal lobe.[14] In contrast, elevated prolactin is not documented in absence epilepsy.[14] In addition, libido is reduced in up to 50% of WWE, more often in right than in left temporal lobe epilepsy.[14] Therefore, a detailed gynecologic history should be part of preconceptional counseling.

Folic acid supplementation

Folic acid supplementation is recommended for all WWE who intend to become pregnant. Folic acid is a necessary coenzyme for the development of white and red blood cells and several central nervous system functions.[16] Folate deficiency during pregnancy is associated with low birth weight, premature delivery, miscarriage, congenital malformations, and preeclampsia.[17,18] In particular, it bears a risk for neural tube defects (NTDs), such as spina bifida.[16] Folate supplementation reduces the risk of NTD by 62% in the general population.[19] The recommended daily dose in primary prevention for healthy women is 0.4 mg/day, starting 4 weeks before and up to 12 weeks of pregnancy. The dose should be increased to 0.6 mg/day for the remaining weeks of gestation and reduced to 0.5 mg/day during lactation.[16] Higher doses (0.8–1 mg/day) are suggested in women with other risk factors, such as known genetic variations in the folate metabolic cycle, smoking, diabetes, obesity, and exposure to medications with antifolate effects.[20]

WWE are faced with twice the risk for fetal malformations compared with the general population (4–6%) depending on the type and dose of ASM.[16] Therefore, the American Academy of Neurology (AAN) recommends preconceptional folate supplementation to reduce the risk of major congenital malformations (MCM) in WWE (Level C).[21] They do not comment on folate dosage.

For WWE considered to have a high-risk pregnancy, some authors recommend high doses of folate supplementation, particularly if the patient has a history of NTDs.[17,22–25]

The American Obstetrician and Gynecologist (ACOG) recommend a daily dose of 4 mg for WWE.[26,27] In Europe, and in particular in the United Kingdom, guidelines consistently recommend preconceptional prophylaxis with a high dose (5 mg) of folic acid,[28,29] because WWE are considered a high-risk group and the only available formulations are 400 µg and 5 mg tablets.[25]

The use of higher doses in older ASMs is justified by a prospective analysis of 104 patients (128 on carbamazepine, 108 on valproate, 25 on phenytoin, 11 on phenobarbital, 13 on lamotrigine and 8 on oxcarbazepine, 9 on others), registered in the *International Registry of Antiepileptic Drugs and Pregnancy* (EURAP) from 1999 to 2004, showing a significant reduction in the risk of spontaneous abortion in WWE taking high folic acid supplementation (5.0–5.4) compared with those receiving low dosage (0.3–0.5).[18]

Indeed, women taking enzyme-inducing ASMs (e.g. strong inducers: carbamazepine, phenytoin; weak inducers: topiramate, oxcarbazepine, eslicarbazepine acetate) have a greater risk of folic acid deficiency during pregnancy compared with the general population.[30,31] Valproate, although not enzyme inducing, interferes with folate absorption and folate-related co-enzymes.[30–32] On the contrary, high-dose folate supplementation might impair brain development: animal studies indicate interference with neuronal connectivity, leading to a hyperexcitable network.[33–35] Normally, fetal folate levels are 2–4 times higher than maternal levels.[33] Results need to be interpreted with caution because doses in this animal study were higher than those taken by humans (even at 5 mg/day).[33] Furthermore, high-dose folate may cause growth retardation and ventricular wall thickness in mice.[36,37]

Although some ASMs interfere with folate, data for an optimal periconceptional dose of folate in WWE are inadequate and not conclusive.[1] Therefore, according to other authors, there is no reason to use higher dosages since there is no evidence that higher dosages are more useful and at least 0.4 mg/day is considered enough.[1]

To summarize, folate supplementation is generally recommended for WWE to prevent NTDs. However, reports from the prospective epilepsy pregnancy registries have failed to demonstrate that periconceptional use of folate is associated with a lower risk of MCMs,[25,38] while an improvement of intelligence quotient (IQ) scores in 6-year-old children of women with epilepsy who began folate before conception and in early pregnancy is reported.[39]

Although for enzyme-inducing and older ASMs high-dose folate supplementation is recommended, we lack clear guidelines about dosing in newer ASMs such as lamotrigine or levetiracetam.[22]

In conclusion, there is no agreement for an optimal periconceptional dose of folate in WWE taking ASMs and no precise indication. Therefore, the dose to be used is between 0.4 and 5 mg and should be evaluated in each specific clinical case.

In addition, folate levels should be measured preconceptionally to detect folate deficiency.[17]

Management of epilepsy during pregnancy and anti-seizure medications: serum level changes, teratogenic profiles, and long-term outcome

Birth defect rates vary between 3% and 5% in the general population.[40,41] WWE exhibit a drug-dependent and dose-dependent higher risk for MCMs compared with the general population,[42] although the majority of WWE gives birth to a healthy child.

Most accurate data on teratogenic risks are obtained from large prospective pregnancy registers, which collected data over the last 20 years and reported outcomes on nearly 20,000 pregnancies under ASM monotherapy cumulatively: *The North American Antiepileptic Drug and Pregnancy Registry* (NAAPR; since 1997, data of 5925 pregnant WWE in monotherapy with the eight most commonly used ASMs in North America published in 2018), *The United Kingdom and Ireland Epilepsy and Pregnancy Register* (UKIEPR; established in 1996, a 2014 publication reported 15 years data of 5206 WWE exposed to monotherapy with valproate, carbamazepine, lamotrigine), *The Australia Register of Antiepileptic Drugs in Pregnancy* (ARAP; began in 1999, reported in 2014 data of 1461 pregnancies on ASM monotherapy), the *Kerala (India) Registry of Epilepsy and Pregnancy* (KREP; established in 1998, published in 2013 its findings of 1021 pregnancies under ASM monotherapy), and *The International Registry of Antiepileptic Drugs and*

Pregnancy (EURAP; established in 1999 in Europe, including now 44 countries from Europe, Oceania, Asia, Latin America, and Africa. In 2019 EURAP reported 7335 pregnancies on monotherapy with eight ASMs).[42] Kerala and the Australian Registry also contribute 40–80% of their pregnancies to EURAP.[43]

The overall objectives of the registries are to assess the risk of MCM after prenatal ASM exposure, collecting data prospectively.[42,43] However, the major differences between registers are whether women self-reporting or physicians are reporting to the registries.[42,43] In particular, in the NAAPR, recruitment is by self-enrollment, and the pregnancy outcome data were self-reported already at 3 months postpartum.[42,43] By contrast, EURAP enrolls women *via* their healthcare provider, and the outcome assessment is at 1 year.[42,43] Thus, these registries carry a certain risk of selection and reporting bias.[42,43] Preconceptional counseling on rarely prescribed ASMs is challenging because data are obtained only from small retrospective case series bearing a high risk of selection and publication bias.

The following section covers different ASMs in alphabetical order, their teratogenic risks, impact on the neurodevelopmental outcome of the child, and changes in drug levels during pregnancy (see Tables 1–3).

The epileptologist weights the teratogenic risks of a given ASM against seizure-associated risks for mother and child, due to the decline of serum levels of many ASMs during pregnancy. We encourage to titrate seizure-free WWE carefully down to the lowest effective dose approximately 1 year before pregnancy and establish a baseline drug level. Drug monitoring is needed, therefore. Usually, serum measurements reflect the total drug amount (free unbound fraction and protein-bound fraction of the drug). To monitor the clinically relevant free concentration, specialized laboratory techniques are required. Thus, changes in the percentage of ASM protein binding remain obscure measuring the total ASM level and therefore dose increase of ASMs are empiric. The EMPiRE (AntiEpileptic drug Monitoring in PREgnancy) study published in 2018 compared 127 women in the therapeutic drug monitoring group *versus* 130 women in the clinical features monitoring group and did not find any significant differences in both groups regarding primary (seizure deterioration) and secondary maternal and fetal outcomes.[44] However, data need careful interpretation due to the relatively small number of participants.

Brivaracetam

Brivaracetam, the 4-*n*-propyl analogue of levetiracetam, is a newer ASM[45] acting with a higher binding affinity for the synaptic vesicle protein 2A.[46] The drug is characterized by low binding to plasma proteins, metabolism by hydroxylation, and renal elimination.[46] Brivaracetam received initial European Medicines Agency (EMA)[47] and Food and Drug Administration (FDA) approval in 2016 for monotherapy or adjunctive therapy in focal epilepsies.[48–50] There is no sign of teratogenicity in rat or rabbit models.[51] Until to date, only three reports of WWE treated with brivaracetam during pregnancy.[51] One woman had idiopathic generalized epilepsy (patient 1) and two had focal epilepsies (patient 2 and patient 3). Brivaracetam doses ranged from 50 to 200 mg/day. One woman had exposure to valproate early in gestation (patient 2) and one to lamotrigine (patient 3); all received folate during pregnancy (patient 1 and patient 2: 4 mg daily and patient 3: 0.8 mg daily). There were no MCMs. Three minor malformations: infantile hemangioma involving thumbs and back (infant patient 2), congenital dermal melanocytosis, and ankyloglossia (infant patient 1) occurred. No data is available regarding long-term neurodevelopmental outcomes. A woman under brivaracetam in monotherapy and another under polytherapy with brivaracetam, lacosamide, and perampanel had only minor changes in concentration/dose ratios of brivaracetam.[52] The few data available are not sufficient to give clinical advice.

Carbamazepine

Carbamazepine is a first-generation ASM and acts as a sodium channel blocker (SCB).[45] Carbamazepine is 75% protein bound and metabolized *via* CYP1A2, CYP2C8, and CYP3A4.[53] Its active metabolite is carbamazepine-10, 11-epoxide.[54] It is approved by the FDA for the treatment of focal epilepsy, trigeminal neuralgia, and acute mania.[55] MCM prevalence with carbamazepine monotherapy varies from 2.6% to 5.5% among EURAP, NAAPR, and UKIEPR.[1,56]

It carries a specific risk for microcephaly and a fetus small for gestational age (SGA).[57] Long-term

outcome, as revealed by the fetal antiepileptic drug exposure and cognitive outcomes (NEAD) study, showed that intrauterine exposure to carbamazepine may be a risk for decreased verbal reasoning.[58] A meta-analysis showed a risk for cognitive developmental delay, psychomotor developmental delay, attention-deficit hyperactivity syndrome, and a high risk for autism and language delay.[11]

Dose-dependent teratogenic effects were identified for carbamazepine in the EURAP[56] and UKIEPR.[38] Preconceptional daily doses ranging from ⩾400 to ⩽1000 mg have a 3.4% MCM risk, comparable to lamotrigine ⩾300 mg and better than phenobarbital <150 mg or valproate <700 mg.[59]

A minor decline in total carbamazepine concentration is reported during trimesters two and three. However, the unbound serum concentrations of its active metabolites (carbamazepine-10,11-epoxide) remain stable.[60] Recent data reported a decrease of 17.3% for carbamazepine (11.56–7.97 μg/L/mg; $p=0.03$) and no significant changes for unbound carbamazepine, carbamazepine-10,11-epoxide.[61]

Therefore, drug monitoring is optional and dosage adjustment during pregnancy or postpartum is not necessary.

We recommend using low-dose carbamazepine therapy only with caution.

Clobazam

Clobazam is a 1.5-benzodiazepine that received FDA/EMA approval in 2011 as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in individuals 2 years or older.[62] It is also used for adjunctive therapy in Dravet syndrome, refractory status epilepticus, and focal epilepsy.[62] Clobazam is often co-administered with other ASMs in the treatment of epilepsy for better seizure control and catamenial epilepsy.[62–65] Clobazam binds to the GABA-A receptor and increases chloride conduction leading to hyperpolarization of the postsynaptic membrane.[66] The drug has a plasma protein binding of 85–91% and undergoes hepatic metabolization to the active *N*-desmethylclobazam and 4-hydroxyclobazam.

Because clobazam is approved as an adjunctive treatment for seizures, data on clobazam monotherapy and the risk of MCM are sparse. Clobazam is not examined in the EURAP[56] and UKIEPR[38] registry; however, data on clobazam in monotherapy ($n=9$) or polytherapy ($n=151$) were reported from the Kerala Registry of Epilepsy and Pregnancy: the MCM rate was 22.2% for monotherapy and 9.4% for overall exposure to the drug.[67] However, the number of pregnancies exposed to clobazam monotherapy is too low ($n=9$) to be informative. In a cohort study of 96 WWE, congenital abnormalities occurred in five (9.4%) babies; two of them had adjunctive treatment with clobazam: hypoplastic kidneys, bilateral cryptorchidism are reported in a child exposed to lamotrigine, clobazam, and both lamotrigine and clobazam respectively.[68]

Finally, a network meta-analysis did not document statistically significant cardiac malformations, hypospadias, cleft lip, or cleft palate but statistically significant prenatal growth retardation.[11,69]

In conclusion, data on malformation risk are sparse and the drug is not recommended for breastfeeding. Based only on a small number of patients, data is not sufficient to inform clinical practice.[69]

Eslicarbazepine acetate

Eslicarbazepine acetate is a second-generation SCB, which enhances the slow inactivation of voltage-gated sodium channels.[55] The prodrug is rapidly metabolized to the pharmacologic active enantiomer S-licarbazepine (95%) and primarily eliminated by renal excretion.[70–74] Its FDA[75] (2013) and EMA (2009)[76] approval comprises monotherapy and adjunctive treatment for focal epilepsies.[77–80] Until 2018, 79 pregnancies with exposure to eslicarbazepine acetate were documented: 28 during clinical trials and 51 from 8 years of postmarketing surveillance. Congenital anomalies were identified in five cases. In three of them, a possible relationship with eslicarbazepine acetate was established.[81] One case of '*de novo*' unbalanced structural chromosomopathy 18 in a woman concomitantly exposed to lamotrigine. Another one had a clubfoot which refers to a mother with a history of alcohol, tobacco, and marijuana use and concomitantly given lacosamide.[81] The third ended with the spontaneous abortion of possibly conjoined twins (unconfirmed diagnosis) in a patient concomitantly exposed to levetiracetam.[81] Add-on eslicarbazepine acetate in 11 of the 15 pregnancies with spontaneous abortion and congenital anomaly.[81] A stable dose–response relationship has been described between eslicarbazepine serum

concentration and reductions in seizures frequency with no interaction by other ASMs.[82] Concerning long-term neurodevelopmental outcome with eslicarbazepine acetate or breastfeeding safety profile, no studies are available.

Although no particular safety problem was identified, we cannot encourage eslicarbazepine acetate in pregnant women due to a lack of data.

Ethosuximide

Ethosuximide is a first-generation ASM acting on T-type calcium channels; its oral bioavailability is above 90% and protein binding is low. Ethosuximide undergoes hepatic metabolization (CYP3A, more than CYP2E or CYP2C/B). The hydroxyethyl derivative is its main inactivated metabolite and is excreted by kidneys as glucuronide[83] ethosuximide add-on to carbamazepine, phenytoin or phenobarbital decreases serum ethosuximide levels.[84] It is approved by FDA and EMA for the treatment of absence seizures.[55,85]

In a systematic review and meta-analysis, ethosuximide showed an increased risk for MCMs [odds ratio (OR) = 3.04, 95% confidence interval (CI) = 1.23–7.07].[5] An older case series ($n = 13$) documented two (15.4%) MCMs (cleft palate).[86]

Ethosuximide bears a specific teratogenic risk for cleft palate [$n = 29$, OR = 22.22, 95% credible interval (CrI) = 4.56–87.64] and club foot ($n = 10$, OR = 12.99, 95% CrI = 1.66–76.39).[5]

There are no data on neuropsychological outcomes for children of mothers taking ethosuximide monotherapy during pregnancy.

Furthermore, there is no clear data on changes in serum level during pregnancy: in a small case series ($n = 10$), serum ethosuximide levels increased, decreased, or remained stable. Serum level increase postpartum was also reported.[86] Another case showed 61% increased clearance during trimester one.[87]

To summarize, we recommend avoiding ethosuximide in WWE, who want to become pregnant, whenever possible.

Felbamate

Felbamate is a dicarbamate derivative[88] approved by the FDA/EMA in 1993[62,89] as add-on therapy in Lennox–Gastaut syndrome patients aged >4 years.[90] It has multiple mechanisms of action, including *N*-methyl-D-aspartate (NMDA) receptor antagonism, GABA enhancement, and sodium channel blocking.[55] Its oral bioavailability is high and its protein binding is low.[55] It is eliminated by renal excretion and oxidative metabolism, with the formation of an intermediate metabolite, atropaldehyde, that has been related to adverse idiosyncratic reaction and serious progressive organ toxicity of felbamate.[88,90] In preclinical studies, felbamate did not show birth defects in rats or rabbits.[91] No congenital anomaly was found in fetuses exposed to felbamate, but the number of exposed fetuses was very low (1–10)[92,93] that no pattern or estimates of risk can be determined.

Due to sparse data on MCMs, lack of data on pharmacokinetics during pregnancy, breastfeeding safety profile, and neuropsychological outcome of the child, we recommend avoiding felbamate in WWE, who want to become pregnant, whenever possible.

Gabapentin

Gabapentin is a second-generation[45] calcium channel blocker. It binds the alpha-2-delta subunit of voltage-gated calcium channels. It has a low bioavailability decreasing in high dosages, due to a saturable amino-acid uptake transporter in the gut.[94] Gabapentin is serum unbound and eliminated by kidneys without metabolization.[53,55] It is FDA/EMA approved for adjunctive treatment in focal seizures only, but most prescriptions result from neuropathic pain.[55,95]

In a meta-analysis, gabapentin ($n = 329$) did not show an increased risk for MCMs (OR = 1.00; 95% CI = 0.47–1.89) but a risk for cardiac malformations.[5] The NAAPR states 1.1% (0.37–3.5) MCM risk ($n = 263$).[96]

However, a recent population-based cohort study ($n = 4642$ pregnancies) did not document an association with MCMs overall. Among 11 newborns exposed to gabapentin only, 6 were born preterm (54.5% *versus* 14% – OR = 7.37, 95% CI = 1.87–30.54; $p = 0.0018$) and 4 were SGA (36.3% *versus* 10% – OR = 5.14, 95% CI = 1.10–20.23; $p = 0.018$).[97] The MCM documented was ventricular septal defect in 2 of 9 (22%) children exposed to gabapentin in trimester one.[97]

Two studies in children exposed to gabapentin *in utero* compared with unexposed children did not

report statistically significant differences in emotional behavior at age 6 ($n=29$)[98] and reported comparable IQ scores ($n=14$).[99] A meta-analysis reveals that gabapentin bears a risk for psychomotor developmental delay (OR=9.0354, 95% CrI=1.00–62.78).[11]

Due to its renal elimination and the higher renal clearance during pregnancy, the need for dose adjustment during pregnancy can be expected. The few data available are not sufficient to inform clinical practice in pregabalin use in WWE who want to become pregnant.

Lacosamide

Lacosamide is a second-generation SCB[45] enhancing, similar to eslicarbazepine acetate, the slow inactivation of voltage-gated sodium channels.[100] Lacosamide has a high oral bioavailability and a linear pharmacokinetics:[100] it is primarily metabolized *via* the hepatic route by demethylation (CYP2C19 in 30%)[101] and in approximately 40% of lacosamide eliminated unchanged *via* renal excretion mechanisms.[82] It is FDA/EMA approved for adjunctive treatment in focal-onset seizures and focal epilepsies in adults.[102,103] Data from preclinical studies found a high incidence of embryonic lethality and malformations.[104] In mice, morphological alterations in the prefrontal cortex, hippocampus, and amygdala were associated with behaviors associated with schizophrenia spectrum disorders.[104] The number of human lacosamide–exposed fetuses is very low (1–10) but without MCMs.[92,105] More recent data from NAAPR quote no MCM risk (0.0%, 95% CI=0.28–13.6).[96] In 2017, normal developmental milestones were reached by three *in utero* infants exposed to lacosamide.[105] Serum concentrations of lacosamide in pregnancy remained fairly stable in a small study.[52] Whereas a decrease was reported in seven pregnancies (lacosamide 200–600 mg/day), through each trimester compared with the baseline without effect on seizure frequency; none of the neonates had MCMs.[106] However, more consistent data come from the recently published MONEAD (Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs) study, reporting a decrease of dose-normalized concentrations during pregnancy of 39.9% for lacosamide (26.14–15.71 μg/L/mg; $p<0.001$).[61]

To conclude, the lack of data does not allow us to draw a firm conclusion about lacosamide use in WWE, who want to become pregnant.

Lamotrigine

Lamotrigine is a second-generation ASM.[45] It is a SCB, inhibiting the release of glutamate more than GABA.[107] Lamotrigine is 55% protein-bound[108] and extensively metabolized *via* UDG-glucuronyltransferase (UGT1A4 and UGT2B7).[109]

Lamotrigine is FDA/EMA approved for focal and generalized seizures.[55,110] It has comparable effectiveness to carbamazepine in focal seizures but is better tolerated.[111]

Lamotrigine bears a 1.9–2.6% risk for MCMs.[1,96] It does not bear risks for specific MCMs.[5] A statistically significant dose-dependent teratogenic effect was identified for lamotrigine in the EURAP register.[56] However, high-dose lamotrigine (400 mg/day) still had a lower risk (non-statistically significant) compared with low-dose valproate (<600 mg/day): 3.4% *versus* 5.0%, respectively.[38] Concerning the long-term outcome, children exposed to lamotrigine *in utero* did not have altered neurocognitive profiles.[112] However, in network analysis ($n=2551$ – several ASMs), lamotrigine was associated with higher odds for autism spectrum disorders (OR=8.88, 95% CI=1.28–112.00). After more restrictive analysis (nonsmoking WWE on lamotrigine monotherapy and high-quality studies), the effect was not statistically significant anymore.[11]

Serum concentrations of lamotrigine and its 2-*N*-glucuronide metabolite decline during pregnancy up to 50–70%.[113,114] A recent data of a prospective, observational cohort study, of drug plasma concentrations in women taking monotherapy or in combination with noninteracting medications, reported that the dose-normalized concentrations during pregnancy were decreased by up to 56.1% for lamotrigine (15.60–6.85 μg/L/mg; $p<0.001$) compared with postpartum value.[61]

A potential benefit regarding maternal (seizure freedom) or fetal (MCM) outcome by monthly blood sampling ($n=127$) compared with clinically driven counseling during pregnancy ($n=130$) was not confirmed by the EMPiRE study in pregnant women with epilepsy who showed at least 25% ASM level decline.[44] A major part of these women were on lamotrigine and seizure-free. The authors did not comment on the dosage of empirically uptitrated ASMs in the clinical decision cohort or on the target serum level

(preconceptional lowest effective dose or accepting a 30% decline in serum level) in the blood sampling cohort. They documented higher umbilical cord concentrations of lamotrigine and levetiracetam in the drug monitoring group, suggesting an (unnecessary) higher up titration in this cohort. We, therefore, still advise taking serum levels regularly (e.g. monthly)[115] during pregnancy starting with the positive pregnancy test. Up-titrating of the drug during pregnancy is essential[1] and serum levels can give good guidance to avoid overdosing.

Serum lamotrigine concentrations return to preconceptional relatively rapidly already the first days after delivery, reaching preconceptional levels usually within 2–3 weeks.[115] In some patients, it may take considerably longer[116,117] and serum measures should be extended according to the slower decay.

Despite its potential risk for autism in children and its significant alterations of serum levels during pregnancy, lamotrigine is still an appropriate ASM for WWE in childbearing age due to its favorable profile for MCMs.

Levetiracetam

Levetiracetam is a second-generation ASM[45] that binds to the synaptic vesicle protein SV2A. Its bioavailability is high, and its protein binding is low. Levetiracetam is minimally metabolized and excreted renally.[55,118] It is licensed for initial monotherapy in focal seizures and add on in generalized epilepsies and myoclonic jerks (EMA/FDA).[55,119] Levetiracetam is most effective in focal seizures, but also in (primary) bilateral tonic-clonic seizures and to a minor extent also in myoclonic seizures, less in absences.[120]

Levetiracetam bears a 0.7–2.8% risk for MCMs among the three large registers.[38,56,121] It does not bear risks for specific MCMs.[5] However, polytherapy does not seem to be associated with increased malformation rates.[122]

This beneficial effect might be due to levetiracetam's impact on apoptosis. Preclinical data suggest triggering of apoptotic neurodegeneration through NMDA-receptor blocking or $GABA_A$ receptor activation. In rat pups, these effects were shown for phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, and valproate.[123] Carbamazepine, topiramate, lamotrigine, and levetiracetam instead do not alter apoptosis in developing rat brains.[124,125] Furthermore, data from developing rat brains underline also the more favorable combination of moderate dosage carbamazepine and levetiracetam, instead of topiramate and phenytoin that is the worst one and showed more apoptosis than phenytoin alone.[124,125]

No negative impact on neurocognitive development in children exposed to levetiracetam *in utero* was documented in a single small study.[99]

Serum concentrations decline during pregnancy by 40–60%.[126–128] Recent data reported a decrease of 36.8% for levetiracetam dose-normalized concentrations during pregnancy.[61] Up-titrating during pregnancy and subsequently down titrating during the first week postpartum seems logical. Due to the relatively small sample size, serum level monitoring on a monthly base[115] during pregnancy,[1] and daily within the first week after birth, is recommended.

Despite its significant changes in serum level during pregnancy, levetiracetam is one of the most appropriate ASMs for WWE in childbearing age due to its favorable profile for MCMs.

Oxcarbazepine

Oxcarbazepine is an SCB that receives FDA/EMA approval for the treatment of focal-onset seizures.[129] It is after oral intake metabolized to eslicarbazepine (or S-licarbazepine) and the inactive R-licarbazepine.[55] Both stereoisomers are eliminated mainly by glucuronidation.[126,130,131] In 248 pregnancies with oxcarbazepine monotherapy and 61 under add-on oxcarbazepine, 2.4% (6/248) MCMs in monotherapy and 6.6% (4/61) with adjunctive therapy were documented.[132] The NAAPR reports a 1.6% MCM risk with oxcarbazepine monotherapy[96] and the EURAP 3.0%.[1,56] Moreover, EURAP provided ORs for other treatments compared with the low-dose lamotrigine in a multivariable analysis including other potential risk factors in addition to ASM: based on this analysis, oxcarbazepine was associated with a risk similar to the lower lamotrigine dose.[56] Finally, a Cochrane review reported a risk of 2.39% in MCMs in 238 children and no increased risk for minor malformations; no data was reported on the relationship between oxcarbazepine dose and malformation rates.[133] From

the available data, oxcarbazepine bears a specific risk for hypospadias.[5,92,134]

Concerning the adverse effect on the child, two cases reported neonatal abstinence syndrome after intrauterine exposure to oxcarbazepine. In the first case, the infant was born to a mother in status epilepticus who was treated with oxcarbazepine 1400 mg/day as monotherapy.[135] The second case is a neonate born to a mother who received oxcarbazepine 300 mg/day throughout her pregnancy.[129] Regarding the long-term effects on child neurodevelopment, data for oxcarbazepine were so limited that firm conclusions cannot be drawn.[129] Oxcarbazepine was significantly associated with increased occurrence of autism/dyspraxia in a meta-analysis.[11] This association disappeared when the analysis was restricted to offspring of WWE and when only studies of high quality and adequate follow-up were considered.[11] In a large population study, no elevated risks were found for oxcarbazepine-exposed children *versus* control or *versus* other ASMs[136–138] in global and specific cognitive outcomes.

Studies on the pharmacokinetics of oxcarbazepine during pregnancy report a serum concentration of its main metabolites and are 36% lower compared with prepregnancy or postpregnancy values.[139–141] The plasma concentration decreased from the first trimester and the lowest concentration observed after week 20.[126]

Data from the MONEAD study recently published reported that the dose-normalized concentrations decrease 32.6% for oxcarbazepine (11.55–7.79 µg/L/mg; $p < 0.001$) and 30.6% for unbound oxcarbazepine (6.15–4.27 µg/L/mg; $p < 0.001$).[61]

Increased seizure frequency during pregnancy was reported in 64–100% of oxcarbazepine pregnancies, and dose adjustments were performed in 86–100%.[141–143] After delivery, the serum concentrations return to baseline within the first 4–8 weeks.[142] Therefore, oxcarbazepine serum level monitoring regularly (e.g. monthly) during pregnancy and daily within the first week of the postpartum is advisable.

In conclusion, the available data regarding MCM risk and long-term outcomes allows us to suggest using oxcarbazepine with caution in pregnancy.

Perampanel

Perampanel is a third-generation ASM[45] with a selective non-competitive antagonism on the glutamate AMPA receptor ion channel.[144,145] Perampanel is licensed as adjunctive treatment of focal seizures in patients aged ⩾4 years (and as monotherapy in the United States), and as adjunctive treatment of tonic-clonic seizures associated with idiopathic generalized epilepsy in patients aged ⩾12 years (and ⩾7 years in the EU), based on Class I evidence.[82,144,146–150] It has high protein binding (96%); it undergoes hepatic metabolism *via* CYP3A4 and is excreted in the feces and the urine.[82]

In 90 pregnancies exposed to perampanel, 43 were full-term pregnancies and 26 were women without other concomitant medications.[151] Adverse effects were reported in 5 of 43 children: low APGAR (Appearance, Pulse, Grimace, Activity, Respiration) score in two, fatal neonatal aspiration in one, cystic fibrosis and congenital deafness in one, and poor sucking reflex and shallow breathing in another.[151] No studies regarding long-term outcomes are available.[151]

No controlled studies have investigated the pharmacokinetics of perampanel in pregnancy; however, dosage should be monitored carefully during pregnancy and after childbirth, with adjustments made on a clinical basis.[82]

The few data available are not sufficient to give clinical advice.

Phenobarbital

Phenobarbital is a first-generation ASM introduced into therapy in 1912 by Hoffmann as monotherapy or adjunctive therapy for partial and generalized tonic-clonic seizures.[152] Its main mechanism of action is binding to the GABA-A receptor and prolonging the opening of the chloride channel.[55] Following oral intake, 80% is absorbed in the gastro-enteric tract and is partially excreted in unaltered form by the kidney (25–50%).[152] Plasma protein binding is approximately 50% and it is metabolized in the liver by N-glucosidation (25%) and aromatic hydroxylation catalyzed by CYP2C9.[153,154] MCM risk reported by the NAAPR for phenobarbital monotherapy (median average dose was 120 mg/day) was 5.5% (11 of 199).[134] In the same report, phenobarbital was associated with a higher risk of

cardiac, urogenital defects, and oral clefts, and in particular from the total of 11 malformations: 1 hypospadias, 5 cardiovascular anomalies, and 4 oral clefts.[134] The EURAP[56] reported MCMs in 6.5% (19/294) of pregnancies. Furthermore, the risk increased was higher at doses of more than 80 mg/day.[56] In particular, in 217 WWE the risk of malformation increased from 5.4% for doses <150 mg/day to 13.7% for doses >150 mg/day.[56]

No report of phenobarbital from the UKIEPR Registry or other registries,[155] probably because of infrequent use of phenobarbital in the United Kingdom. Finally, a Cochrane meta-analysis reported a risk of MCMs based on data from 23 studies of 709 children exposed to phenobarbital of 7.10%.[133] The risk ratio of WWE compared with the offspring of women without epilepsy ($N = 345$ *versus* 1591) was 2.84. Low risk was considered for phenobarbital doses of 80 mg/day or less. However, at higher doses, phenobarbital was only second to valproate in terms of comparative risk.[156] Whereas for the cognitive and psychomotor developmental delay outcomes, children exposed to the combination of carbamazepine, phenobarbital, and valproate had greater odds to harm than those who were not exposed to these ASMs.[5]

The free and total levels of phenobarbital decrease by up to 50% during pregnancy.[157] Plasma concentrations during the third trimester are on average 70% of the preconception levels.[157,158]

In conclusion, we suggest avoiding phenobarbital in WWE who want to become pregnant, whenever possible.

Phenytoin

Phenytoin, a hydantoin derivative, is the classical SCB.[159] It was introduced in 1939 and is primarily used for the treatment of tonic-clonic/focal seizures and status epilepticus.[160,161] The drug is metabolized by cytochrome P450 enzyme to 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (4′-HPPH)[159] and it is 90–95% protein-bound. The EURAP registry[56] reported data on 125 phenytoin pregnancies with doses ranging from 30 to 730 mg/day. There were 6.4% MCMs (one NTD; five cardiac; two others). Regarding other registries, the NAAPR registry reported a risk of 2.6% (95% CI = 1.5–4.5);[96] the UKIEPR had a risk of 3.7%.[38] Furthermore, the Motherisk Registry,[162,163] which included women treated with phenytoin for epilepsy and other conditions, reported a risk of 8.8% (3/34) for those exposed to phenytoin, and another report found[164] nine MCMs in 141 (6%) phenytoin-exposed children, which was not significantly different from the control group (5/33). In a Cochrane review, the risk of MCM for 1279 children exposed to phenytoin, based on data from 25 studies, was 5.38%.[133] It bears a specific risk for cleft palate and club foot.[5] The majority of included studies did not investigate the relationship between phenytoin dose and malformation outcome. The small number of phenytoin-exposed pregnancies and conflicting results of these reports limit the available data. Several authors reported lack of dosage-dependent teratogenicity,[162,163,165] and others[164,166] found an increased risk from 2.0% (<200 mg/day) to 4.1% (>300 to 500 mg/day) in 33 pregnancies.

No significant associations were found between neurodevelopment and exposure to phenytoin.[11] Phenytoin serum levels decrease from the first trimester until the third trimester by 55–61% (18–31% for free phenytoin).[54,117,167] On the contrary, clearance of phenytoin increased from the first trimester, probably secondary to decreased protein binding, and become statistically significant only during the third trimester.[54,117] For these reasons, determining free phenytoin plasma concentrations appears to be preferable for ASM monitoring during pregnancy.[54,117]

In conclusion, we recommend avoiding phenytoin in WWE during pregnancy, whenever possible.

Pregabalin

Pregabalin, a third-generation ASM,[45] structurally related to gabapentin, has higher and dose-independent bioavailability. It is not protein-bound and is excreted renally.[55,168] It is FDA/EMA approved for adjunctive treatment in focal seizures but is most often used for anxiety or mood disorders, and neuropathic pain.[55,169]

Data on pregabalin exposure during pregnancy are limited. Three case studies reported conflicting results: first a malformation rate of 3.3% comparable to the general population ($n = 30$).[57,170] Second, an increased risk for MCMs ($n = 116$, 6.0% *versus* 2.1%; OR = 3.0, 95% CI = 1.2–7.9),[171] and a smaller case series ($n = 30$) reported odds toward diverse adverse outcomes (one ventricular septum defect),

however not statistically significant (1/13, 7.7%).[97] The NAAPR documented 51 pregnancies with 1.9% MCM (95% CI = 0.28–13.6).[96]

Early neurodevelopmental outcomes were not impaired in pregabalin-exposed children in a French nationwide observational study.[136]

Due to its renal elimination and higher renal clearance during pregnancy, the need for dose adjustment during pregnancy can be expected.

Although data on teratogenicity are encouraging, we cannot encourage the use of pregabalin in WWE due to sparse data and lack of sufficient data on the neurocognitive outcome of the children.

Topiramate

Topiramate is a second-generation ASM[45] with multiple mechanisms of action: blocking of voltage-gated sodium channels, AMPA (alpha-amino-3-hydroxy-methylisoxazole-4-propionic acid) and kainite receptor antagonism, as well as GABA augmentation.[55] Topiramate is 15% protein-bound and eliminated renally without major metabolism.[172] It is FDA/EMA approved for migraine and focal and generalized seizures.[55,173]

The risk of MCMs is 4.4% (95% CI, 2.9–6.3) according to the NAAPR.[96] There is a particularly high association of topiramate exposure and smaller head circumference (18.5%). It bears a specific risk for microcephaly (OR = 4.8, 95% CI = 2.5–9.3), SGA (OR = 3.1, 95% CI = 1.9–5.3),[57] and cleft palate (OR = 6.12, 95% CrI = 1.89–19.05).[5]

The EURAP registry reported 3.9% (95% CI = 1.5–8.4) MCMs.[56] Topiramate had a dose-dependent risk for oral clefts with a relative risk for doses ⩽100 mg (OR = 1.64, 95% CI = 0.53–5.07) compared with doses >100 mg (OR = 5.16; 95% CI = 1.94–13.73).[174] In a systematic review and meta-analysis, topiramate had an increased risk for MCMs (OR = 1.90; 95% CI = 1.17–2.97).[5] In polytherapy, topiramate also has a positive dose relationship with teratogenicity risk ($p = 0.025$).[122]

There are no statistically significant data on neuropsychological outcomes of the children.[11]

Serum levels decline up to 30–40% during trimester three.[63] The MONEAD study reported a decrease during pregnancy for topiramate of 13.77 µg/L/mg compared with postpartum values to 29.83 µg/L/mg ($p = 0.18$).[61] Therefore, serum level monitoring regularly (depending on seizure freedom and serum level decline)[115] is advisable. If augmented during pregnancy, serum sampling might be useful for postpartum dose reduction as well.

Due to its teratogenic effects, low-dose topiramate should only be used with caution in WWE who want to become pregnant.

Valproic acid/valproate

Valproate is a first-generation antiepileptic drug.[45] It has multiple mechanisms of action including GABA-ergic system and inhibition of different enzymes in the tricarboxylic acid cycle.[175] Valproate is approximately 90% protein-bound and cleared by hepatic glucuronidation through UDP Glucuronosyltransferase (UGT1A3, UGT2B7) and several cytochrome P-enzymes (CYPs).[115,176]

In vitro, valproate leads to DNA fragmentation or gene expression pointing to apoptosis.[177]

Although used in focal and generalized seizure types, it is most effective in generalized epilepsies (myoclonic jerks, absences, and bilateral tonic-clonic seizures)[178] and is superior to lamotrigine, topiramate, and levetiracetam in this indication.[179,180]

The risk for MCMs varies between 6.7% and 10.3%.[38,56,96] The risk of valproate is higher compared with levetiracetam or lamotrigine and is dose-dependent with a cut-off for high-dose exposure between 500 and 650 mg/day.[1,38,56] Among the MCMs associated with valproate are NTDs, orofacial/craniofacial, skeletal, and limb malformations.[133] Furthermore, valproate bears a specific teratogenic risk for hypospadias (OR = 2.58, 95% CI = 1.24–5.76), cleft palate (OR = 3.33, 95% CrI = 0.66–11.80), and club foot (OR = 3.26, 95% CrI = 1.43–8.25).[5,181]

On top, valproate bears a risk for minor congenital malformations, for example, facial dysmorphic abnormalities (epicanthal folds, flat nasal bridge, small nose with anteverted nostrils a long upper lip with relatively shallow philtrum, a relatively small mouth with downturned angles, and a thin upper

vermilion border). A complex of symptoms including facial dysmorphic features in children exposed to valproate *in utero* is defined as the fetal valproate syndrome. The facial abnormalities are often associated with minor skeletal abnormalities, such as finger abnormalities and sternum deformity or cryptorchidism. The risk for the syndrome is more likely considered intrinsic and not dose-dependent.[182]

Besides its risk for MCMs, valproate carries an intrinsic risk for neurocognitive impairment of the children. Children exposed to valproate exhibit a reduced IQ, memory, attention, or language skills compared with non-exposed children.[39] It carries a significant risk for autism (OR = 17.29, 95% CrI = 2.40–217.60), cognitive developmental delay (OR = 7.40, 95% CI = 3.00–18.46), psychomotor developmental delay (OR = 4.16, 95% CrI = 2.04–8.75), and language delay (OR = 7.95, 95% CrI = 1.50–49.13).[11] Although risks are dose-dependent, no 'safe' dose can be identified.

After the FDA and EMA warning against valproate treatment of girls and women of childbearing age, the International League Against Epilepsy (ILAE) published a position paper on how to deal with valproate in this population and when to use valproate despite the FDA and EMA warnings. Among those, the most important are (3): 'For seizure (or epilepsy) types where valproate is the most effective treatment, the risks and benefits of valproate and other treatment alternatives should be discussed'. (4): 'valproate should not be prescribed as a first-line treatment for focal epilepsy'. (5): 'valproate may be offered as a first-line treatment for epilepsy syndromes where it is the most effective treatment, including idiopathic (genetic) generalized syndromes associated with tonic-clonic seizures'.[183]

Furthermore, the Summary of Product Characteristics (SmPC) states that valproate 'should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated'.[183]

When valproate is the most appropriate treatment option, the patient and caregiver must be fully informed of the risks associated with valproate use during pregnancies and the possibility of limitations of prenatal screening methods.[183] Every effort should be made to ensure that the patient and caregiver have truly understood these risks.[183]

We encourage obtaining written informed consent and reevaluate the treatment regime at least once a year and immediately if the patient wishes to become pregnant within the next 2 years. A subsequent pregnancy should then be planned 1 year after successful therapy change, only.

In some European countries (e.g. Italy and Germany), there are 'Informative note for doctors', a letter from the Drug Agency or Public Health Ministry explicitly warning doctors not to use valproate in (pintended) pregnancies because of its teratogenicity, and availability of other treatment options.[184,185]

In contrast to total serum concentrations declining up to 40% during late pregnancy, unbound serum concentration remains unchanged.[186] Drug monitoring (only free fraction reasonable) and dose alterations are not necessary[187] during pregnancy or the postpartum period.

Summarized we advise against the use of valproate in women with childbearing potential. Although it has high teratogenic risks and negative impact on the neuropsychological development of the children, there is no evidence for changing the ASM regime in a seizure-free WWE on valproate during pregnancy. In contrast, there are signs of the risk of losing seizure control.[188]

Zonisamide

Zonisamide, a second-generation ASM,[45] is a benzisoxazole derivative drug,[189] approved by FDA in 2000 and EMA in 2005, as an adjunct treatment for focal seizures.[82,190]

It has a dual mechanism of action: a weak inhibition of enzymes and modulation of GABAergic and glutamatergic neurotransmission *via* alteration of voltage-sensitive sodium and calcium channels.[191] After oral intake, it is rapidly absorbed, 50% bound to plasma proteins and is eliminated predominantly by biotransformation.[192]

The first report on the teratogenic effect was assessed in one study with 26 children exposed to zonisamide *in utero*.[193] They found two cases of MCMs when zonisamide add-on to first-generation ASMs: anencephaly was detected in one case at 16 weeks of gestation and the atrial septal defect was detected in another case at 37 weeks

of gestation. Furthermore, the NAAPR reported a risk of MCM of 0.9% in 218 pregnancies.[96] Instead, the UKIEPR[194] reported data on 112 cases of first-trimester exposure to zonisamide, including 26 in monotherapy; from those, there were 3 MCMs in monotherapy and 5 in polytherapy. Furthermore, there was a high rate of infants born SGA.[194] Low birth weight and length were also reported in 98 zonisamide-exposed pregnancies.[195]

Regarding pharmacokinetics changes during pregnancy, two case reports found a decrease of zonisamide serum concentrations during pregnancy by 20–40%, a rise postpartum by 45% within 9 days.[196,197] These findings were confirmed by several other reports.[87,197,198] The MONEAD study reported a decrease in dose-normalized concentrations of zonisamide during pregnancy of 29.8% (40.12–28.15 µg/L/mg; $p < 0.001$) compared with postpartum values. The decrease of zonisamide serum concentration was associated with an increase of seizures in 33% of WWE, especially in the second and third trimesters.[198] In addition, breakthrough seizures occurred in 40% of the pregnancies (including polytherapy) in WWE who were seizure-free in the prepregnancy year and dose adjustments were frequently necessary during pregnancy.[143,198]

In conclusion, due to sparse data on teratogenicity, an unfavorable breastfeeding risk profile, and lack of data on neuropsychological development of the children, we cannot encourage the use of zonisamide in WWE who intend to become pregnant.

See Tables 1–3.

Management of epilepsy during pregnancy and prenatal diagnosis: gynecological management of WWE

Pregnancy management in WWE handling teratogenicity risk, seizure control, and prenatal diagnostics is multidisciplinary (epileptologist, gynecologist/obstetrician). We lack consistent guidelines on prenatal ultrasound frequency. The ILAE, the AAN, the European Academy of Neurology (EAN), or the German Neurological Society (DGN) recommends specific prenatal neuro-sonographic controls. We rely on nationwide recommendations. In Italy, for instance, ultrasound morphologic evaluation is recommended at gestational week 19th to 21st screening for fetal anatomies.[200,201] In Austria, prenatal diagnostics are free of charge and include obstetric investigations at gestational weeks 17–20, 25–28, 35–38, ultrasonography at gestational weeks 8–12, 18–22, 30–34, laboratory investigations before gestational week 16, and internal medicine investigation at week 17–20.[202]

Ultrasonographic screening for NTDs is mandatory at gestational week 13 (identify anencephaly and myelomeningocele).[200] Diagnostic accuracy in detecting spina bifida is lower. At gestational week 24, it has a 98% diagnostic sensitivity.[203,204]

Cardiac defects are screened by maternal ultrasonography and by fetal echocardiography. Fetal echocardiography after gestational week 20 identifies cardiac defects in 80–90% of cases.[201,205,206] Its diagnostic sensitivity depends on the type of anomaly: intraventricular and atrial defects are difficult to identify; valve stenosis may not manifest until the third trimester.[200] The risk of cardiac defects is closely related to the thickness of nuchal translucency and is particularly high when nuchal translucency is above the 99th percentile in the fetus without chromosomal abnormalities.[200,207]

Orofacial clefts are detected by bi-dimensional ultrasound imaging around gestational week 20 with a diagnostic sensitivity of 27%.[208] Sensitivity increase after gestational week 20 and if ultrasonography is performed by a tri-dimensional technique: cleft lip and cleft palate are diagnosed in 100% and 90% of cases, respectively.[209,210]

Finally, in the evaluation of MCMs risk, it is important to consider the presence of a positive family history MCMs. In these cases, genetic counseling must be considered.

Vitamin K prophylaxis and birth mode

Since 1958, more than 40 cases of the early hemorrhagic disease have been reported in newborns of mothers taking enzyme-inducing ASMs (e.g. carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone). Different authors questioned oral vitamin K administration since then.[211,212] Vitamin K supplementation for bleeding prophylaxis was recommended both to the mother, in the last 2 weeks before delivery (10–20 mg/day), and to the child (1 mg).[213] Data from 662 pregnancies in WWE who used enzyme-inducing ASMs *versus* 1324 nonepileptic pregnancies (1334 neonates)

Table 1. Anti-seizure medication and risks for major congenital malformations (MCMs)..

	Prevalence % (95% CIs)	**Prevalence % (95% CIs)**	**Prevalence % (95% CIs)**	**Prevalence *n/n* (%)**	**OR (95% CrI)**	**Specific MCMs**
ASM	EURAP[56]	NAAPR	UKIEPR[1]	Others	Veroniki *et al.*[5]	
BRV				0,[a,51] 0[b,51]		
CBZ	5.5 (4.5–6.6)	2.7 (1.9–3.8)[96]	2.6 (1.9–3.5)		1.37 (1.10–1.71)	Microcephaly[57]
CLB				2/9 (22.2),[67] 5/96 (9.4)[67]	3.48 (0.52–13.84)	
CLZ		1.6 (0.41–6.5)[96]			1.13 (0.59–2.02)	Hypospadias[5]
ESL				[a,81]		
ETX				2/13 (15.4)[86]	3.04 (1.23–7.07)	Cleft palate,[5]club foot[5]
FBM				0[b,91]		
GBP		1.1 (0.37–3.5)[96]		2/9 (22.0)[97]	1.0 (0.47–1.89)	Cardiac[5]
LCM		0.0 (0–7.4)[96]		0,[a,92,105] high[b,105]		
LEV	2.8 (1.7–4.5)	1.8 (1.2–2.7)[96]	0.7 (0.2–2.4)		0.72 (0.43–1.16)	
LTG	2.9 (2.3–3.7)	1.9 (1.5–2.6)[96]	2.3 (1.8–3.1)		0.96 (0.72–1.25)	
OXC	3.0 (1.4–5.4)	1.6 (0.7–3.8)[96]			1.32 (0.72–2.29)	Hypospadias[5,92,134]
PB	6.5 (4.2–9.9)	5.5 (3.1–9.6)[96]			1.83 (1.35–2.47)	Cleft palate[5]
PER				Possible[a,151]		
PGB		1.9 (0.28–13.6)[96]		1/30 (3.3),[57] 28/477 (5.9)[170] 1/13 (7.7),[97] 7/116 (6.0)[171]		
PHT	6.4 (2.8–12.2)	2.6 (1.5–4.5)[96]	3.7 (1.2–10.2)		1.69 (1.30–2.17)	Cleft palate,[5] club foot[5]
PRM					1.22 (0.65–2.12)	Cleft palate,[5] club foot,[5] hypospadias[5]
TPM	3.9 (1.5–8.4)	4.4 (2.9–6.3)[96]	4.3 (1.5–11.9)		1.9 (1.17–2.97)	Cleft palate,[5] microcephaly[57]
VGB					2.27 (0.49–7.93)	
VPA	10.3 (8.8–12.0)	9.2 (6.5–13.0)[121]	6.7 (5.4–8.3)		2.93 (2.36–3.69)	NTD,[133] cleft palate,[5] club foot,[5] hypospadias[5]
ZNS		0.9 (0.46–1.8)[96]	13.0 (4.5–32.1)	3/26 (11.5)[194]		

95% CI, confidence interval; 95% CrI, credible intervals; ASM, anti-seizure medication; BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CLZ, clonazepam; ESL, eslicarbazepine-acetate; ETX, ethosuximide; EURAP, International Registry of Antiepileptic Drugs (AED) and Pregnancy; FBM, felbamate; GBP, gabapentin; LCM, lacosamide, LEV, levetiracetam; LTG, lamotrigine; MCM, major congenital malformations; NAAPR, North American AED Pregnancy Register; NTD, neural tube defects; OR, odds ratio; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; PRM, primidone; TPM, topiramate; UKIEPR, United Kingdom and Ireland Epilepsy and Pregnancy Register; VGB, vigabatrine; VPA, valproic acid; ZNS, zonisamide.
Superscript numbers: references.
[a]Insufficient data.
[b]Data from animal studies only.

Table 2. Anti-seizure medication and recommendation for use in girls and women with epilepsy in childbearing age.

Anti-seizure medication	Use in WWE
Brivaracetam	[a]
Carbamazepine	With caution
Clobazam	Avoid[a]
Clonazepam	Avoid[a]
Eslicarbazepine-acetate	[a]
Ethosuximide	Avoid[a]
Felbamate	Avoid[a]
Gabapentin	[a]
Lacosamide	[a]
Levetiracetam	Recommend
Lamotrigine	Recommend
Oxcarbazepine	With caution
Phenobarbital	Avoid
Perampanel	Avoid
Pregabalin	[a]
Phenytoin	Avoid
Primidone	Avoid
Sulthiam	Avoid[a]
Tiagabine	Avoid[a]
Topiramate	With caution
Vigabatrine	Avoid[a]
Valproate	Avoid
Zonisamide	[a]

WWE, girls and women with epilepsy in childbearing age.
[a]Insufficient data.

– in particular, of the 667 neonates, 463 were exposed to carbamazepine, 212 to phenytoin, 44 to phenobarbital, 11 to primidone, and 7 to oxcarbazepine[211] – do not support the hypothesis that maternal enzyme-inducing ASMs increase the risk for bleeding, as confirmed also recently by the AAN in 2015.[22] So there is no inadequate evidence regarding the vitamin K prophylaxis.

Finally, concerning the birth mode of WWE pregnancies, there are no specific indications for elective cesarean delivery, and vaginal delivery is generally recommended.[200] Only the presence of high-frequency seizure during pregnancy and high risk for seizures during labor are indications for cesarean.[214,215] Furthermore, epidural anesthesia is recommended either during labor or cesarean delivery and may even lower the risk of seizures by reducing stress and pain.[200] Finally, the use of prostaglandins for induction of labor is not contraindicated. The risk of obstetric complications is similar to that of the general population.[214–217]

The risk of occurrence of seizures during delivery is rare.[218] In the EURAP register, the percentage of women who experienced seizures during labor was 2.6% of patients on lamotrigine and carbamazepine, 1.9% of patients on phenobarbital, and 1.4% on valproate.[219] The patient should be advised to take their ASM at a regular time.[218] Hyperventilation and maternal exhaustion should be avoided because these conditions could exacerbate a seizure in the mother.[218] A venous access should be prepared for the timely administration of benzodiazepines (e.g. clonazepam or midazolam) in the case of a seizure.[220,221] If a generalized tonic-clonic seizure occurs, a continuous cardiotocography (CTG) should be performed and the fetus should be monitored to prevent respiratory complications,[218,220,221] as generalized tonic-clonic seizures are associated with fetus hypoxia.[220] Finally, WWE should deliver in a center with adequate facilities for maternal and neonatal resuscitation.[220]

Puerperium

ASMs, which have been up titrated during pregnancy, can be reduced empirically by 50% within the first 3 days postpartum, reaching preconceptional dosages after approximately 1 week. However, it might be advisable to keep the dosage a little higher than preconceptional to address sleep deprivation. Data are abundant for lamotrigine but especially seldom prescribed ASMs (e.g. pregabalin) require individual decision making when up titrated during pregnancy.

Sleep deprivation is a risk factor for seizure recurrence. The immediate postpartum period is critical, therefore. The risk of seizure-related injuries for mother and child can be addressed

Table 3. Changes in anti-seizure medication serum levels during pregnancy and breastfeeding safety profile.

ASM	Levels	%	sz	Adaption	Breastfeeding
BRV					[a]
CBZ	↔[1]			No	2[199]
CLB					4[199]
CLZ					4[199]
ESL			Yes[82]	Likely[a]	[a]
ETX	↓ Possible[87]	61[87]			[a]
FBM					4[199]
GBP	↓ Likely[a]			Likely[a]	3[199]
LCM	↔[52]/↓[106]		No[106]	[a]	[a]
LEV	↓[1]	40–60[1]		Yes	3[199]
LTG	↓[1]	<69[1]		Yes	3[199]
OXC	↓[1]	36–62[1]	Yes[140–142]	Yes	3[199]
PB	↓[157]	70[157]			4[199]
PER					[a]
PGB	↓ Likely[a]			Likely[a]	3[199]
PHT	↓[116]	56[116]			2[199]
PRM					4[199]
TGB					3[199]
TPM	↓[1]	<30[116]		Likely	3[199]
VGB					3[199]
VPA	↔[1]			No	2[199]
ZNS	↓[198]	<35[198]	Yes[198]	Yes	4[199]

ASM, anti-seizure medication; BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CLZ, clonazepam; ESL, eslicarbazepine-acetate; ETX, ethosuximide; FBM, felbamate; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; PRM, primidone; TGB, tiagabine; TPM, topiramate; VGB, vigabatrine; VPA, valproic acid; ZNS, zonisamide.
Superscript numbers: references, ↓ decline, ↔ stable, change in %, sz: breakthrough seizures in case of decline yes or no, adaption: dosage adaption during pregnancy and subsequently postpartum recommended, breastfeeding: safety levels: '2 – safe', '3 – moderately safe', or '4 – possibly hazardous' for breastfeeding.
[a]Insufficient data.

by different life modification factors: first, it is advisable for the sleep-deprived mother not to carry her newborn free but move it in a bedside cot on wheels indoors. Second, using a baby stroller instead of carrying the baby in a baby sling outdoor and third, preferring escalators to stairs is advisable. Furthermore, changing diapers on a pad on the floor instead of a baby changing table avoids dropping. Babies do not need a daily bath. Instead washing with a facecloth on a pad reduces drowning risk. The bathtub should be preserved for other family members. Breastfeeding should

be performed comfortably in the middle of a large bed, preferable to a chair.

Peri-/postpartum depression is more frequent in WWE (26.7%) than in the overall population (18.9%, $p < 0.001$).[222] It is often unrecognized and undertreated.[222] Screening and psychotherapy should be performed regularly yet before delivery.[223]

Breastfeeding

The benefits of breastfeeding, for both mother and child, are widely documented and acknowledged.[224] Despite these benefits, only 42% of WWE breastfeed at 3 months,[225] and women with epilepsy discontinue breastfeeding more often than women without epilepsy.[226] It presents high variability depending on different factors such as the misconception that drugs taken by the mother are retained in the breast milk.[225,227–231] Education about the safety and benefit of breastfeeding might be underrecognized by patients,[232,233] obstetricians, and pediatricians. Patients are most afraid of ASM side effects (42.0%) but frequent seizures (14.9%) and insufficient breast milk supply (14.4%), as well as discouragement from social support (13.8%) and maternal or child health problems (11.2%), are also important issues.[234]

Mothers having seizures are less likely to continue breastfeeding.[234] A beneficial effect of formula nutrition is the fact that the nocturnal care can be shared between the partners, and sleep deprivation of the mother is reduced. However, pumping breast milk during the day to maintain milk supply and a partner feeding the child during the night can assure both less sleep deprivation for the mother and the benefit of breast milk over formula nutrition for the child.

Different methods are described in the literature to calculate the child's exposure to maternal drugs during breastfeeding and among these, the milk/plasma (M/P) ratio is the most known.

The M/P ratio is the relationship between drug concentrations in the breast milk *versus* maternal plasma: an M/P ratio greater than 1 indicates that the drug is concentrated in breast milk, but it does not always reflect the child's actual level of exposure.[235]

In clinical practice, these methods may not be easily obtainable and, in general, there are limited safety data for specific ASMs during lactation based on clinical experience, and case reports on observed side effects.[224]

A recommended literature regarding breastfeeding and medications is the regularly revised 'Medications and Mother's Milk' by Hale *et al.*[199]

In this manual, drugs are classified into five lactation risk categories, ranging from 'Safest' to 'Contraindicated' (L1–L5) and the most ASMs can be divided into three main risk categories: 'L2 – safe', 'L3 – moderately safe', or 'L4 – possibly hazardous.

'Safe' ASMs are those that present a moderately high degree of protein binding in plasma, a low degree of penetration into breast milk, and a reported M/P ratio ranging from 0.01 to 0.7. See Table 3.[236,237]

However, adverse effects are described in case reports using phenytoin in combination with other ASMs, hepatotoxicity, and thrombocytopenia with maternal valproate use and liver dysfunction and reduced weight gain in breastfed infants of mothers using carbamazepine as monotherapy.[238–242]

'Moderately safe' ASMs are listed in Table 3. These ASMs have a low degree of protein-binding in plasma (from 15% of topiramate to 55% of lamotrigine and oxcarbazepine), low molecular weight, and a reported M/P ratio from 0.1 to 2.0.[126,243–250]

Lamotrigine is an example of infants' limited capacity to metabolize due to an immature hepatic UDP glucuronidation, which is associated with a reduced plasma protein-binding, and could result in high serum concentrations in the breastfed neonate.[243] Adverse effects in infants are rarely reported and include mild thrombocytosis and a case report describes serious apnea in an infant whose mother used high doses of lamotrigine after delivery.[251,252]

Topiramate and gabapentin have a dose-related effect: maternal doses at 200 mg daily or less of topiramate and up to 2100 mg daily of gabapentin

produced low infant serum concentrations and no adverse effects in the neonates.[246,247,253–255]

Data about levetiracetam come from a recent study of 20 breastfeeding women and 21 infants.[256] Infant levetiracetam exposure *via* the breast milk was close to the safety thresholds and the adverse effect commonly reported is somnolence.

There are no reports of data on side effects of oxcarbazepine and tiagabine, but due to limited data, these ASMs are still classified as moderately safe.[224] See Table 3.

At least, 'possibly hazardous' ASMs are listed in Table 3. These ASMs are characterized by an M/P ratio from 0.3 to 2.8, a low degree of protein-binding, and high excretion into breast milk.[236,257–262] Furthermore, these drugs present an extremely long half-life and could accumulate in breastfed infants with repeated or continuous maternal administration.[253,261,263] Sedative effects such as drowsiness and reduced weight gain have been reported with ethosuximide[86] and benzodiazepines such as diazepam and clonazepam.[253] Caution is recommended during breastfeeding with primidone, zonisamide, and felbamate.

We lack an evidence-based safety profile of lacosamide, perampanel, and brivaracetam.

Lacosamide dosages up to 400 mg/day appeared to not adversely affect development in three infants who were breastfed for 7–9 months.[105,264] M/P ratios of brivaracetam, lacosamide, and perampanel are 0.71, 0.83, and 0.13, respectively.[52]

In addition to the short-term effects on the child related to breastfeeding, data on the long-term neurodevelopmental effects are important. See Table 1.

The cognitive development in 199 children at 3 years old who were breastfed by mothers taking ASMs (carbamazepine, lamotrigine, phenytoin, or valproate monotherapy) compared with children who were not breastfed was unimpaired: no significant difference in the IQs between the two groups.[225] At age 6 years, the authors reported similar results for 181 children, with an overall significantly higher IQ in breastfed *versus* not breastfed children.[58] Others confirmed that long-term breastfeeding is safe on cognition. However, they found a higher risk of impaired fine motor skills in children of mothers taking ASMs compared with the reference group at 6 months.[265,266] See Table 4.

Discussion and conclusion

The management and the care of WWE start in the preconception phase with the planning of pregnancy, childbirth, postpartum, and breastfeeding. The choice of the ASM should be appropriate for epilepsy syndrome and must consider the teratogenic potential of the drug. Valproate and other ASMs with high teratogenic potential should be avoided. Individualized ASM baseline concentration should be established using the minimal effective dose preferably in monotherapy. Teratogenic risk remains low if an appropriate ASM monotherapy is prescribed and most WWE will give birth to a healthy child. Folate supplementation is strongly recommended to prevent NTDs; nevertheless, clear guidelines about dosing are lacking. Besides teratogenicity, the neurocognitive outcome of the child remains an issue. Although bearing risk for autism spectrum disorders, lamotrigine and levetiracetam are the two most preferred ASMs for WWE due to their favorable safety profile for MCMs. During pregnancy, management involves gynecologists, obstetricians, and geneticists. We recommend at least three clinical visits if seizures are stable. Increased ASM clearance during pregnancy causes significant fluctuations in several ASMs among them levetiracetam and lamotrigine. Up-titrating is essential to avoid breakthrough seizures. A balance between the lowest possible dose to challenge teratogenicity but prevent (tonic-clonic) seizures is the goal. Recent evidence underlines the careful clinical-driven decision making in drug dosing equally effective to serum sampling.[44] However, the recent results of a prospective, observational cohort study (MONEAD) suggest that therapeutic drug monitoring should begin early in pregnancy and that increasing doses of these anticonvulsants may be needed throughout the course of pregnancy. Most information on teratogenic effects comes from the EURAP, NAARP, and UKIEPR registries. Valproate in mono or polytherapy is associated with the highest risk of adverse neurodevelopmental outcomes.[11] Morphologic ultrasonographic evaluation is recommended preconceptionally, and once each trimester. More detailed sonography (organ screening) is

Table 4. Impact of anti-seizure medications on the neurocognitive outcome of the child.

	Neurocognitive	Cognitive developmental delay	Autism/dyspraxia	Psycomotor delay	Language delay	ADHS
ASM	Impairment	OR (95% CrI)[11]	OR (95% CrI)[11]	OR (95% CrI)[11]	OR (95% CrI)[11]	OR (95% CrI)[11]
CBZ	Verbal reasoning↓[39]	2.07 (0.82–5.48)	5.76 (0.76–73.43)	1.68 (0.85–3.41)	4.32 (0.81–26.93)	2.32 (0.70–7.86)
CLB				2.81 (0.21–22.20)		
CLZ			6.51 (0.47–112.40)	2.23 (0.47–9.62)		
GBP	IQ↔ emotion↔[a,99,98]	1.46 (0.04–13.48)		9.03 (1.00–62.78)		
LCM	Schizophrenia[b,105]					
LEV	None[99]	3.42 (0.65–16.4)	3.64 (0.00–223.30)	0.27 (0.00–4.26)		
LTG	None[39]	0.93 (0.09–5.10)	8.88 (1.28–112.00)	1.86 (0.72–4.76)	4.36 (0.68–25.41)	1.63 (0.43–6.06)
OXC			13.51 (1.28–221.40)			
PB		1.36 (0.18–7.02)				1.29 (0.25–6.21)
PHT		2.55 (0.72–8.55)	7.09 (0.02–397.07)	2.84 (0.97–7.93)	1.06 (0.22–5.08)	0.63 (0.07–4.07)
PRM		2.15 (0.31–12.26)				
TPM		3.34 (0.45–16.53)		3.89 (0.41–24.27)		
VPA		7.4 (3.00–18.46)	17.29 (2.40–217.60)	4.16 (2.04–8.75)	7.96 (1.5–49.13)	2.82 (0.82–9.93)

ADHS, attention-deficit hyperactivity syndrome; ASM, anti-seizure medication; Autism, autism spectrum disorders; CBZ, carbamazepine; CLB, clobazam; CLZ, clonazepam; CrI, credible intervals; GBP, gabapentin; IQ, intelligence quotient; LEV, levetiracetam; LTG, lamotrigine; OR, odds ratio; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; TPM, topiramate; VPA, valproic acid.
Superscript numbers: references, ↓ impaired, ↔ normal.
[a]Insufficient data.
[b]Data only from animal studies.

Box. Key points for management of women with epilepsy (Adapted from Voinescu PE and Pennell PB[267]).

Planning for pregnancy
- Choose the appropriate ASM for the epilepsy syndrome, with the lowest teratogenic risk
- Titrate to the lowest effective dose, establish individualized therapeutic ASM baseline
- Prefer monotherapy over polytherapy
- Some ASMs are preferable (LTG, LEV) while some should be avoided (VPA, PB, PHT)
- Folic acid supplementation is recommended to prevent NTDs. High dose is suggested in the presence of history of NTDs but also in women taking antiepileptic drugs, especially enzyme-inducing ASMs (CBZ, PHT, TPM, OXC) as well as VPA

Management of epilepsy during pregnancy
- Plan at least three clinical visits if seizures are stable, otherwise more frequent visits
- Monitor ASMs serum levels, adjust dosage if levels declines or seizure frequency increases
- Prenatal ultrasonographic organ screening is recommended at the 19th to 21st gestational week
- Data on vitamin K prophylaxis and perinatal bleeding are controversial
- Vaginal delivery is generally recommended as well as epidural anesthesia and the use of prostaglandins
- Cesarean is indicated when poor seizure control during pregnancy and high risk for seizures during labor could compromise delivery and increase the risk of complications

Postpartum
- Drug monitoring is suggested in the first week postpartum to adjust the ASMs dosage
- To allow the possible effect of sleep deprivation during breastfeeding, it might be advisable to remain the ASM dosage slightly higher than preconceptional
- Breastfeeding is highly recommended with implementation of strategies to lessen sleep deprivation

ASM, anti-seizure medication; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; NTD, neural tube defects; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproic acid.

recommended, if available. Recent data do not support peripartum vitamin K prophylaxis. Vaginal delivery is generally recommended.[200,214,215] Indications for a cesarean can be given when poor seizure control during pregnancy and high risk for seizures during labor could compromise delivery and increase the risk of complications. Epidural anesthesia is also recommended such as the use of prostaglandins for induction of labor.

After discharge, serum concentration of ASMs reach preconceptional levels in around 14–21 days. We recommend empirically reduction approximately twice the up titrated dose within half a week and nearly down to preconceptional levels after 1 week. We advise repeated drug monitoring during the first week postpartum, to adjust ASMs dosages and weekly controls within the first 4 weeks. To allow the possible effect of sleep deprivation during breastfeeding, it might be advisable to remain the ASM dosage slightly higher than preconceptional level. Most ASMs are compatible with breastfeeding with a safe or moderately safe risk of side effects in the infant, but it is important to observe the infant and monitor the possibility of side effects and, in these cases, consider mixed nutrition with formula milk supplement. The literature presents also supporting data that breastfeeding does not have any negative impact on the neurodevelopment of the child.

Author contributions

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