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REVIEW ARTICLE

Therapeutic Drug Monitoring of Antiepileptic Drugs in Women with Epilepsy Before, During, and After Pregnancy

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Abstract

During pregnancy, the pharmacokinetics of an antiepileptic drug is altered because of changes in the clearance capacity and volume of distribution. These changes may have consequences for the frequency of seizures during pregnancy and fetal exposure to antiepileptic drugs. In 2009, a review was published providing guidance for the dosing and therapeutic drug monitoring of antiepileptic drugs during pregnancy. Since that review, new drugs have been licensed and new information about existing drugs has been published. With this review, we aim to provide an updated narrative overview of changes in the pharmacokinetics of antiepileptic drugs in women during pregnancy. In addition, we aim to formulate advice for dose modification and therapeutic drug monitoring of antiepileptic drugs. We searched PubMed and the available literature on the pharmacokinetic changes of antiepileptic drugs and seizure frequency during pregnancy published between January 2007 and September 2018. During pregnancy, an increase in clearance and a decrease in the concentrations of lamotrigine, levetiracetam, oxcarbazepine's active metabolite licarbazepine, topiramate, and zonisamide were observed. Carbamazepine clearance remains unchanged during pregnancy. There is inadequate or no evidence for changes in the clearance or concentrations of clobazam and its active metabolite *N*-desmethylclobazam, gabapentin, lacosamide, perampanel, and valproate. Postpartum elimination rates of lamotrigine, levetiracetam, and licarbazepine resumed to pre-pregnancy values within the first few weeks after pregnancy. We advise monitoring of antiepileptic drug trough concentrations twice before pregnancy. This is the reference concentration. We also advise to consider dose adjustments guided by therapeutic drug monitoring during pregnancy if the antiepileptic drug concentration decreases 15–25% from the pre-pregnancy reference concentration, in the presence of risk factors for convulsions. If the antiepileptic drug concentration changes more than 25% compared with the reference concentration, dose adjustment is advised. Monitoring of levetiracetam, licarbazepine, lamotrigine, and topiramate is recommended during and after pregnancy. Monitoring of clobazam, *N*-desmethylclobazam, gabapentin, lacosamide, perampanel, and zonisamide during and after pregnancy should be considered. Because of the risk of teratogenic effects, valproate should be avoided during pregnancy. If that is impossible, monitoring of both total and unbound valproate is recommended. More research is needed on the large number of unclear pregnancy-related effects on the pharmacokinetics of antiepileptic drugs.

1 Introduction

Treatment of epilepsy during pregnancy faces multiple challenges. Clinicians have to find a balance between the risk of increased seizure frequency for both the mother and child on the one hand and fetal exposure to antiepileptic drugs (AEDs) on the other hand. Most pregnant women with epilepsy (WWE) will deliver a healthy child, but some women experience an increase in seizure frequency during pregnancy, which can be harmful especially to the fetus. Fetal

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Key Points

Pharmacokinetics of antiepileptic drugs (AEDs) may change during pregnancy and this may result in a change of effect.

It is advised to determine the AED concentration twice before conception for every woman with epilepsy to obtain a pre-pregnancy reference concentration (RC) for targeted therapeutic drug monitoring during and after pregnancy.

Dose adjustment during pregnancy should be considered in combination with risk factors if the AED concentration deviates 15–25% from the RC and should always be considered if the AED concentration deviates more than 25% from the RC.

loss has been reported as a result of prolonged seizures, and poorer congenital development has been associated with frequent tonic-clonic seizures during pregnancy [1, 2]. Therefore, clinicians pursue a stable AED concentration that is effective enough to avoid seizures. However, maintaining a stable AED concentration during and after pregnancy is difficult owing to the alteration of AED pharmacokinetics including increased volume of distribution, elevated renal clearance, and induction of hepatic metabolism. [3–5]. Therefore, it is important to determine the reference concentration (RC) for every AED before pregnancy, which provides guidance for clinicians for the personalized management of individual WWE during and after pregnancy [6].

Many studies on fetal exposure, adverse drug reactions, and Major Congenital malformations associated with AED use during pregnancy have been published in the past decade [1, 7–13]. However, much less is known about the pharmacokinetics of specific AEDs during pregnancy compared with pre-pregnancy. In addition, little is known about the influence of the changed AED pharmacokinetics on seizure frequency in pregnant WWE. Moreover, guidelines on therapeutic drug monitoring (TDM) and dose adjustments during pregnancy are unclear and differ between countries. In 2009, Harden et al. [3] published on behalf of the American Academy of Neurology (AAN) and the American Epilepsy Society (AES) a practice parameter update of management issues in pregnant WWE. Since that review, new information on included AEDs has become available and new, not included AEDs are increasingly being prescribed. This narrative review aims to provide an updated overview of changes in the pharmacokinetics of AEDs and advice on TDM of 11 different AEDs before, during, and after pregnancy.

2 Literature Search

This narrative review includes six AEDs most frequently prescribed for the treatment of epilepsy during pregnancy in European countries: carbamazepine (CBZ), levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), topiramate (TPM), and valproate (VPA) [8] and five other AEDs: clobazam (CLB), gabapentin (GBP), lacosamide (LCM), perampanel (PER), and zonisamide (ZNS), which are currently increasingly prescribed in men and women with uncontrolled epilepsy. Seven of these AEDs are discussed by Harden et al. [3]. A literature search was performed to determine whether new publications concerning pharmacokinetics and changes in seizure frequencies during pregnancy of these seven AEDs had been published since the AAN/AES publication and whether TDM might be of any benefit. The remaining four AEDs (CLB, LCM, PER, and ZNS) that are used less frequently, but are expected to be increasingly prescribed in Europe in pregnant women, have been added to obtain an up-to-date overview.

The following strategies were endorsed to find the relevant literature. First, a systematic PubMed search using the MeSH terms ‘drug name’, ‘pregnancy’, and ‘drug monitoring’ per drug was employed. Second, the MeSH terms ‘pregnancy’, ‘epilepsy’, ‘anticonvulsants’, and ‘drug monitoring’ were used. In addition, studies that referred to Harden et al. [3] were selected. The practice parameter update of the AAN and AES formed the starting point for this updated review [3]. Because Harden et al. [3] included studies until October 2007, any literature published between January 2007 and September 2018 was screened for the seven drugs that Harden et al. [3] reviewed. All available relevant literature about the remaining four drugs and relevant articles for background information was included despite the year of publication. Articles were excluded on title and abstract, whereby articles that were not written in English and reviews were excluded from this study. Monotherapy studies were preferred above polytherapy studies because monotherapy studies provide better insight into drug-specific influences during pregnancy. Polytherapies were only included on the premise that the available monotherapy evidence was insufficient and drug–drug interactions were not expected. These polytherapy data are marked ([a]) in Tables 1 and 2. Reference lists of obtained records were screened to obtain additional studies not identified through database searching. Uptodate.com [14] provided further drug information on the pharmacokinetics of AEDs in the non-pregnant state. A total of 508 records were identified using our search strategy. After removing the duplicates, 373 unique records were screened on title, abstract, and year of publication, which resulted in 37 potentially relevant full-text articles. After reading the full text, eight full-text articles were excluded and 15

additional studies were included from cross-references, which resulted in 44 included studies (Fig. 1).

Tables 1 and 2 provide an overview of the pharmacokinetic changes of AEDs, seizure frequency, and recommendations on TDM before, during, and after pregnancy based on the included studies. When Harden et al. [3]. were unable to present pharmacokinetic changes or recommendations, new information and recommendations were formulated if possible and displayed in italics.

3 Impact of Pregnancy on Antiepileptic Drugs

3.1 Carbamazepine

One study compared seizure frequency during pregnancy with pre-pregnancy [15]. In 22% of the pregnancies, patients experienced an increase in seizures and in 33% of the pregnancies, patients experienced a decrease in seizures during pregnancy compared with pre-pregnancy. In 44% of the patients, the seizure frequency remained stable [15]. Other reports of seizure control during pregnancy agree that most pregnant WWE do not have increased seizure frequency during the trimesters of pregnancy if CBZ is used for seizure control [16, 17]. As a consequence, dose adjustments are not often performed during pregnancy [15, 17]. Clearance of CBZ or CBZ-epoxide is not significantly changed during pregnancy [15, 16]. Unbound CBZ concentrations are increased throughout pregnancy and the total and unbound CBZ-epoxide concentrations slightly decreased during the first trimester and normalized afterwards [15]. A relationship between seizure frequency and changed concentrations of total or unbound CBZ concentrations could not be demonstrated [15–17]. Data on postpartum pharmacokinetics are missing.

3.2 Clobazam

One study reported that patients experienced seizures in 72% of the pregnancies with CLB use (most polytherapy) [18]. Data of seizure frequency during pregnancy compared with pre-pregnancy seizure frequency are lacking. Pregnant WWE treated with CLB had more than twice the propensity to have seizures when compared with pregnant WWE who were using LTG, VPA, LEV, or TPM monotherapy [18]. Clobazam was often co-administered with other AEDs in the treatment of epilepsy for better seizure control [19–21]. None of the studies have published dose adjustments or changed pharmacokinetics of CLB and its active metabolite *N*-desmethylclobazam during and after pregnancy.

3.3 Lamotrigine

Use of an oral contraceptive (OC) before conception in combination with LTG treatment is associated with a reduced LTG concentration by approximately 50% [22, 23]. Several studies observed worsening of seizure control and increasing dose and/or addition of another AED (16–100%) more often among LTG pregnancies than in other AED pregnancies [16, 24–27]. In 19–38% of the pregnancies, the patients experienced an increase in seizures during pregnancy [16, 26, 28] and in 10–33% of the pregnancies, a decrease in seizures during pregnancy [16, 17, 26, 28] compared with pre-pregnancy. In 28–71% of the pregnancies, the seizure frequency remained stable [16, 18, 26, 28]. The clearance of total LTG strongly increased during pregnancy and the total LTG concentration significantly decreased [16, 25, 26, 29, 30]. Postpartum, the elimination rate returned to normal within the first few weeks [25, 30–32]. Studies suggest that the decline in total LTG plasma concentration is partly caused by a pregnancy-related enhanced hepatic glucuronidation and partly by an increased renal clearance [25, 29, 30].

3.4 Levetiracetam

Some studies report a high rate of seizure occurrence and dose increases and/or addition of another AED among LEV pregnancies with inter-individual variability [16, 21, 33–36]. A relatively large retrospective study reported that 47% of the pregnant WWE taking LEV monotherapy experienced more seizures during pregnancy compared with 1 year before pregnancy [16]. More data on seizure frequency compared with pre-pregnancy seizure frequency are still lacking. A more recent study emphasizes the potential benefit of TDM during LEV pregnancies due to the magnitude of LEV clearance between LEV pregnancies [4]. In addition, pharmacokinetic changes of LEV were observed during and after pregnancy [16, 21, 33–36]. The total LEV concentration decreased during pregnancy and showed a maximal decline in the third trimester (48–60%) [21, 33–37], owing to an increase of total LEV clearance during pregnancy [4, 16, 35, 36] that returned to normal in the first few weeks after delivery [21, 33, 34]. In addition, there is some evidence for better seizure control when LEV extended release is administered more frequently than once or twice daily [35, 36].

3.5 Oxcarbazepine

In 64–100% of the OXC pregnancies, seizure frequency increased during pregnancy compared with pre-pregnancy seizure frequency [27, 38]. Consequently, dose adjustments were performed in 86–100% of the pregnancies [27, 38]. The total plasma concentration of OXC's active metabolite LIC

Table 1 Changes in pharmacokinetics and concentrations of antiepileptic drugs (AEDs) during pregnancy

AED	Absorption and bioavailability	Distribution	Metabolism	Elimination	Changes in AED concentration
Carbamazepine	Non-pregnant state: slow absorption from GI tract [6, 14] Bioavailability: 70% [6, 14] During pregnancy: no data available	Non-pregnant state: moderate protein bound [15, 55]	Non-pregnant state: almost completely metabolized into CBZ-EPO [14, 56] AED polytherapy: PB, PHT, and PRM enhance the metabolism of CBZ[56] Enzyme-inducing AEDs and VPA may increase CBZ Cl [56] During pregnancy: Insufficient evidence	Non-pregnant state: Elimination half-life is variable: 12–17 h [14] During pregnancy: no significant changes in unbound CBZ Cl or CBZ-EPO Cl [15, 16] Postpartum elimination: no data available	*Total and unbound CBZ and CBZ-EPO concentrations did not change substantially during pregnancy* [15]
Clobazam	Non-pregnant state: rapid and extensive absorption [14] Bioavailability: 87% [14] During pregnancy: no data available	Non-pregnant state: Highly protein bound [55]	Non-pregnant state: hepatic CYP metabolism into active metabolite dmCLB [14, 57, 58] During pregnancy: no data available	Non-pregnant state: Elimination half-life 10–30 h; dmCLB 36–46 h [59] During pregnancy: no data available Postpartum elimination: no data available	No data available
Gabapentin	Non-pregnant state: variable dose-dependent, saturable absorption [14] Bioavailability: inversely proportional to dose due to saturable absorption: 27–60% [14] During pregnancy: No data available	Non-pregnant state: not protein bound [55]	Non-pregnant state: not metabolized and eliminated unchanged by renal excretion [14] During pregnancy: not influenced [14]	Non-pregnant state: elimination half-life 5–7 h [14] During pregnancy: no data available Postpartum elimination: no data available	No data available
Lacosamide	Non-pregnant state: completely absorbed [14] Bioavailability: ~100% [14] During pregnancy: no data available	Non-pregnant state: Minimally protein bound [55]	Non-pregnant state: for 30% metabolized into inactive O-DES-LCM for 20% into a uncharacterized metabolite [14] 40% eliminated unchanged by renal excretion [14] During pregnancy: no data available	Non-pregnant state: Elimination half-life: 13 h [14] During pregnancy: no data available Postpartum elimination: no data available	No data available

Table 1 (continued)

AED	Absorption and bioavailability	Distribution	Metabolism	Elimination	Changes in AED concentration
Lamotrigine	Non-pregnant state: absorption is rapid and almost complete [14, 27] Bioavailability: 98% [14, 27] During pregnancy: no data available	Non-pregnant state: Moderate protein bound [25, 27, 55]	Non pregnant state: hepatic and renal metabolism, > 75% metabolized via glucuronidation [14] Metabolism may be induced by co-medication CBZ [60] OC reduces LTG concentration by 50% [22, 23] During pregnancy: enhanced hepatic glucuronidation by UGT enzymes [25, 30]—increased 2-N-GLUC/LTG ratio [25]	Non pregnant state: Elimination half-life 25–33 h [14] Co-medication with VPA decreases the LTG Cl [60] During pregnancy: strongly increased Cl of LTG [16, 25–27, 29, 30] and increased concentration of 2-N-GLUC throughout pregnancy [25] *Possible trend of higher LTG Cl in white patients* [26] Postpartum elimination: *elimination rate drops to normal—in first few weeks* [25, 30–32]	Highly decreased total LTG concentrations throughout pregnancy [25, 27, 30]
Levetiracetam	Non-pregnant state: absorption is rapid and almost complete [14] Bioavailability: ~ 100% [14] During pregnancy: no data available	Non-pregnant state: minimally protein bound [34, 55]	Non-pregnant state: extrahepatic hydrolysis [14, 34] Mainly excreted unchanged [34] During pregnancy: conflicting data	Non-pregnant state: elimination half-life 6–8 h [14] During pregnancy: increased Cl during pregnancy[a] [16, 35, 36] Peak Cl in 1st trimester [4] Peak Cl in 2nd trimester [16] Increased renal blood flow may contribute to decline in LEV concentration [34] LEV Cl may change in the same woman across two pregnancies [36] Postpartum elimination: *elimination rate drops to normal—in first few weeks*[a] [21, 33, 34]	Concentrations decrease throughout pregnancy especially during the 3rd trimester [21, 33–36] Case report: 20% reduction in LEV plasma concentrations in 1st trimester and 48% reduction in 3rd trimester vs. 2 months prior to pregnancy [21] Decline in total LEV concentration of 50–60% in 3rd trimester[a] [33, 34, 37]
Oxcarbazepine	Non-pregnant state: almost completely absorbed [14, 27] Bioavailability: No data available, elimination is not first order [6] During pregnancy: no data available	Non-pregnant state: OXC and LIC: Moderate protein bound [27, 32, 38, 55]	Non-pregnant state: OXC is a pro-drug and almost completely metabolized into the active metabolite LIC [14, 32] LIC is primarily glucuronidated [14, 32] During pregnancy: Enhanced hepatic glucuronidation by enzyme induction [25, 30, 32]	Non-pregnant state: elimination half-life 8–10 h of LIC [14, 32] During pregnancy: Increased Cl of LIC with a peak Cl in 2nd and 3rd trimesters [4, 27] Postpartum elimination: *elimination rate returned to normal within the first 4–8 weeks after delivery* [38]	Gradual decreased plasma concentration of LIC throughout pregnancy [38] Case series ($n = 14$): 26% reduction in LIC plasma concentration in 1st trimester, 37% in 2nd trimester, and 38% in 3rd trimester vs. pre-pregnancy[a] [38]. One polytherapy with TPM Non-significant increase of postpartum C/D by 7% [38]

Table 1 (continued)

AED	Absorption and bioavailability	Distribution	Metabolism	Elimination	Changes in AED concentration
Perampanel	Non-pregnant state: rapid and complete absorption [14] Bioavailability: no data available During pregnancy: no data available	Non-pregnant state: highly protein bound [55]	Non-pregnant state: oxidation by CYP3A metabolism [14] During pregnancy: no data available	Non-pregnant state: elimination half-life ~ 105 h [14] During pregnancy: no data available	No data available
Topiramate	Non-pregnant state: rapid absorption [14] Bioavailability: ~ 80% [14] During pregnancy: no data available	Non-pregnant state: minimally protein bound [19, 55]	Non-pregnant state: mainly renally excreted unchanged [14, 61] During pregnancy: conflicting data	Non-pregnant state: Elimination half-life 19–23 h [14] During pregnancy: *increased Cl in 2nd and 3rd trimesters* [4] *Presumably increased Cl through increase in renal blood flow and decrease in tubular reabsorption* [19] Postpartum elimination: no data available	*Gradually decline in TPM serum concentrations throughout pregnancy*[a] [39] *Decreased serum concentration by 30–40% in 2nd and 3rd trimesters*[a] [19, 39, 40] *Extensive variability in the extent of decreased D/C ratio on both monotherapy or polytherapy*[a] [19]
Valproate	Non-pregnant state: bioavailability: ~ 90% [14] During pregnancy: no data available	Non-pregnant state: highly protein bound [55]	Non-pregnant state: extensively hepatic glucuronide conjugation and mitochondrial beta-oxidation [14] During pregnancy: Conflicting data	Non-pregnant state: elimination half-life 9–19 h [14] During pregnancy: insufficient evidence Possibly unchanged [4, 41] Postpartum elimination: no data available	Conflicting and insufficient data on changes of unbound VPA concentrations [41] Extensive variability in decline of total C/D ratio during pregnancy and postpartum [41]
Zonisamide	Non-pregnant state: rapid and complete [14] Bioavailability: ~ 100% [14] During pregnancy: *A possible reduced GI absorption is suggested* [42]	Non-pregnant state: Moderate protein bound [55, 62]	Non-pregnant state: metabolized through various hepatic pathways [14, 62] During pregnancy: *Assumed to be increased* [42]	Non-pregnant state: elimination half-life ~ 63 h [14] 15–30% unchanged renal elimination [62] During pregnancy: *increased Cl* [16, 42, 43] Case report: *Cl in 1st, 2nd, and 3rd trimesters increased by 108%, 142%, and 117%, respectively* [16] Postpartum elimination: no data available	*Decreased throughout pregnancy* [42, 43] *ZNS concentrations decreased > 40% during pregnancy with inter-individual variability*[a] [42] *Case report: ZNS concentration declines in 27 weeks of 2nd trimester* [43] *Case reports: Increased postpartum ZNS concentrations by 33–35% within 9 days after delivery* [63]

New information and recommendations were formulated if possible and displayed in italics

2-N-Gluc 2-*N*-glucuronide, *CBZ* carbamazepine, *CBZ-EPO* carbamazepine-epoxide, *C/D* concentration/dose, *Cl* clearance, *CLB* clobazam, *CYP* cytochrome P450, *dmCLB N*-desmethyl-clobazam, *D/C ratio* dose/concentration ratio, *GI* gastrointestinal, *LTG* lamotrigine, *LEV* levetiracetam, *OC* oral contraceptive, *O-DES-LCM O*-desmethyl-lacosamide, *OXC* oxcarbazepine, *PB* phenobarbital, *PHT* phenytoin, *PRM* primidone, *TPM* topiramate, *UGT* uridine diphosphate glucuronosyltransferase, *VPA* valproate, *ZNS* zonisamide

[a]Polytherapies were included

Table 2 Overview of dose adjustments, seizure control, and advice on therapeutic drug monitoring (TDM) during pregnancy in women with epilepsy (WWE) taking antiepileptic drugs (AEDs)

AED	Dose adjustment and dose frequency	Seizure control during pregnancy and delivery	Conclusions and our advice
Carbamazepine	Low rate of dose increase or addition of AED [15, 17] Dose increase is necessary in 3% of the pregnancies [17]	Most pregnancies without deteriorated seizure frequency, compared with pre-pregnancy [15–17] Increased frequency in 15% of the patients in 2nd and 3rd trimester [17] Seizure free during pregnancy in 51–67% pregnancies ($n=155$; $n=914$) [17, 18] *No clear relationship between seizures and changes in total or unbound CBZ or CBZ-EPO* [15–17]	*Minimal changes in CBZ and CBZ-EPO concentrations and the lack of a relationship with seizures do not necessitate measurements of CBZ and CBZ-EPO during pregnancy* [15]. *It should be reconsidered if routine TDM of CBZ during pregnancy is necessary. During pregnancy, we advise to change CBZ treatment depending on clinical features, seizure risks, and previous doses. When the WWE experience seizures during pregnancy, total trough concentrations of CBZ and CBZ-EPO could be measured for extra information on changing the CBZ dose until more evidence for discouraging monitoring of CBZ during pregnancy is obtained* *Practical advice* Before conception: measure the total CBZ and CBZ-EPO serum trough concentrations two times if the patient is on stable seizure control and determine the RC for comparison purposes During pregnancy: adjust the CBZ dose depending on clinical features, seizure risks, and previous doses After delivery: adjust the CBZ dose depending on clinical features, seizure risks, and previous doses
Clobazam	No data available	*Seizure free during pregnancy in 28% of the pregnancies ($n=124$)* [18][a] *More than twice the propensity to have seizures during pregnancy as mono- or polytherapy when compared with women using LTG, VPA, LEV, or TPM* [18][a]	*There is a lack of sufficient data on the pharmacokinetic changes of CLB during pregnancy. When CLB is indicated, we advise monitoring during pregnancy when clinical features deteriorate or the risk of seizure occurrence is increased* *Practical advice* Before conception: measure the total and unbound CLB and dmCLB trough concentrations two times if the patient is on stable seizure control with a minimal dose to determine the RC During pregnancy: measure the total and unbound CLB and dmCLB serum trough concentration when necessary and maintain the RC by adjustment of the dose After pregnancy: measure the total and unbound CLB and dmCLB serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy

Table 2 (continued)

AED	Dose adjustment and dose frequency	Seizure control during pregnancy and delivery	Conclusions and our advice
Gabapentin	No data available	No data available	*There is a lack of sufficient data on the pharmacokinetic changes of GBP during pregnancy. When GBP is indicated, we advise monitoring during pregnancy when clinical features deteriorate or the risk of seizure occurrence is increased* *Practical advice* Before conception: measure the total GBP serum trough concentration two times if the patient is on stable seizure control with a minimal dose to determine the RC During pregnancy: measure the total GBP serum trough concentration when necessary and maintain the RC by adjustment of the dose After delivery: measure the total GBP serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy
Lacosamide	No data available	No data available	*There is a lack of sufficient data on the pharmacokinetic changes of LCM during pregnancy. When LCM is indicated, we advise monitoring during pregnancy when clinical features deteriorate or the risk of seizure occurrence is increased* *Practical advice* Before conception: measure the total LCM trough concentration two times if the patient is on stable seizure control with a minimal dose to determine the RC During pregnancy: measure the total LCM serum trough concentration when decided necessary and maintain the RC by adjustment of the dose After delivery: measure the total LCM serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy

Table 2 (continued)

AED	Dose adjustment and dose frequency	Seizure control during pregnancy and delivery	Conclusions and our advice
Lamotrigine	High rate of dose increase or addition of AED [16, 17, 25, 27, 30, 31] Dose increase or addition of AEDs is performed in 16–100% of the pregnancies [16, 17, 25, 27, 30, 31]	Inter-individual variability compared with pre-pregnancy frequencies Increased frequency in 19–38% of the pregnancies [16, 26, 28] Decreased frequency in 10–33% of the pregnancies [16, 17, 26, 28] Remained stable in 28–71% of the pregnancies [16, 18, 26, 28] *LTG is associated with an increase in seizures during pregnancy compared with older AEDs such as CBZ or VPA* [24] Seizure frequency seems to be increased when the LTG concentration decreased to lower than 0.65 of the RC [26]	Because of inter-individual variability, a high rate of dose adjustments, and increased clearance, routine TDM of LTG is advised before, during, and after pregnancy *Practical advice* Before conception: if the WWE is using OCs before planning pregnancy, measure the total LTG serum trough concentration twice to determine the RC on OC use. Thereafter, reduce the LTG dose by 50% at the same time of discontinuing the OC. After 1 month, repeated monitoring and adjustment of the LTG dose is advised until the WWE is on stable seizure control. For women not using OCs, measure the RC of the total LTG serum trough concentration two times while using a minimum dose During pregnancy: measure the total LTG every 4 weeks and maintain the RC by gradual adjustment of the dose After delivery: measure the total LTG serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy
Levetiracetam	High rate of dose increase or addition of AED[a] [16, 21, 33–35] Dose increase in 3rd trimester is common[a] [33–35] High frequency of LEV administration should be considered[a] [35, 36]	*Inter-individual variability* [4] Increased seizure frequency during the trimesters of pregnancy [16, 21, 33–36] Performs as well as CBZ and VPA in controlling seizures [24] Seizure free during pregnancy in 68% of the pregnancies ($n=82$) [24]	More research on LEV use during pregnancy is needed. Because of the inter-individual variability, a high rate of dose adjustments and increased clearance during the whole pregnancy, routine TDM of total LEV is advised before, during, and after pregnancy *Practical advice* Before conception: measure the total LEV serum trough concentration two times if the patient is on stable seizure control with a minimal dose to determine the RC During pregnancy: measure the total LEV serum concentration every 4 weeks and maintain the RC by adjustment of the dose After delivery: measure the total LEV serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy

Table 2 (continued)

AED	Dose adjustment and dose frequency	Seizure control during pregnancy and delivery	Conclusions and our advice
Oxcarbazepine	High rate of dose increase [27, 38] Dose increases is performed in 86% pregnancies ($n=14$), with an average increase of 1.5 times [38][a]One polytherapy with TPM Case reports ($n=2$): Increase of dose or addition of AED in 100% of the pregnancies [27][a]Two polytherapies with LTG	Seizure frequency increased in 64–100% of the pregnancies compared with pre-pregnancy frequency ($n=2$; $n=14$) [27, 38][a]Three polytherapies Seizure free during pregnancy in 36–47% of the pregnancies ($n=17$; $n=14$) [18, 38] Breakthrough seizure occurred in 36% of the pregnancies in WWE who were seizure free prior to pregnancy [38]. In 50% of the pregnancies, the seizure frequency was at least doubled compared with pre-pregnancy [38] Highest risk of seizure deterioration in the 2nd or 3rd trimester [38] *More than twice the propensity to have seizures during pregnancy as mono- or polytherapy when compared with women who were using LTG, VPA, LEV, or TPM* [18] Observed trend between LIC plasma concentration and seizure deterioration [38]	More research on OXC use during pregnancy is needed. Because of the observed trend between LIC plasma concentration and seizure deterioration, routine TDM during pregnancy is advised before, during, and after pregnancy. *Practical advice* Before conception: measure the total LIC serum trough concentration two times and test the liver function if the patient is on stable seizure control with a minimal dose to determine the RC of LIC During pregnancy: measure the total LIC serum trough concentration every 4 weeks and maintain the RC by adjustment of the dose of OXC. Consider if routine monitoring of the liver function once every trimester is required for the individual patient After delivery: measure the total LIC serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy
Perampanel	No data available	No data available	*There is a lack of sufficient data on the pharmacokinetic changes of PER during pregnancy. When PER is indicated, we advise monitoring during pregnancy when clinical features deteriorate or the risk of seizure occurrence is increased* *Practical advice* Before conception: measure the total and unbound PER trough concentrations two times if the patient is on stable seizure control with a minimal dose to determine the RC During pregnancy: measure the total and unbound PER concentrations when decided necessary and maintain the RC by adjustment of the dose After delivery: measure the total and unbound PER serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy

Table 2 (continued)

AED	Dose adjustment and dose frequency	Seizure control during pregnancy and delivery	Conclusions and our advice
Topiramate	*High rate of dose increase or addition of AED*[a] [39] *Dose increase or addition AED is performed in 2nd or 3rd trimester*[a] [39] *An average 42 and 52% dose increase is needed in 2nd and 3rd trimester to maintain the RC*[a] [39]	*Seizure frequency increased in 47% of the pregnancies during the 2nd or 3rd trimester*[a] [39] *In 27% of pregnancies, seizure frequency also increased during the 1st trimester*[a] [39] *Observed relationship between decreased TPM concentrations and increased seizure frequency* [4] *TPM treatment is associated with women having more seizures during pregnancy than CBZ or VPA treatment* [24]	*More research on TMP use during pregnancy is needed. Because of the recent observed trend between TPM plasma concentration and seizure deterioration, routine TDM during pregnancy is advised before, during, and after pregnancy* *Practical advice* Before conception: measure the total TPM serum trough concentration two times if the patient is on stable seizure control with a minimal dose to determine the RC During pregnancy: measure the total TPM serum trough concentration every 4 weeks and maintain the RC by adjustment of the dose After delivery: measure the total TPM serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy
Valproate	Relative low rate of dose increase or addition of AEDs [17, 41] Dose increase is performed in 7% of the pregnancies [17]	Seizure frequency increased in 13% of the patients during the 2nd and 3rd trimesters compared with the 1st trimester ($n=974$) [17] Seizure free during pregnancy in 60–75% of the pregnancies[a] ($n=974$; $n=38$) [17, 41] Variable seizure frequency[a] [41]	*VPA is recommended to be avoided during pregnancy and effective contraception to be used during treatment. If avoiding use during pregnancy is not possible and the patient is well controlled on low doses of VPA not exceeding 500–600 mg/day, routine TDM of VPA is advised before, during and after pregnancy* [10, 53, 54] *Practical advice if VPA cannot be avoided during pregnancy* Before conception: measure the total and unbound VPA serum trough concentrations two times if the patient is on stable seizure control with a minimal dose to determine the RC. All women receiving VPA treatment must be carefully informed about the teratogenic risks and limitations of prenatal screening [53] During pregnancy: Measure the total and unbound VPA serum concentrations every 4 weeks and maintain the RC of the unbound VPA serum concentration by adjustment of the dose After delivery: measure the total and unbound VPA serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy

Table 2 (continued)

AED	Dose adjustment and dose frequency	Seizure control during pregnancy and delivery	Conclusions and our advice
Zonisamide	*High rate of dose increase* [42] *Dose increase is performed 19 times in 10 pregnancies* [42] *Successful dose increase from 200 to 300 mg/day without seizure occurrence* [43]	*Seizure frequency increased during pregnancy (n = 23)*[a] [42] *Seizure frequency increased in 33% of the pregnancies on monotherapy ZNS, especially in the 3rd trimester (n = 6)* [42] *Seizure frequency increased in 9% of the pregnancies during the 1st trimester and 26% in the 2nd trimester as well as in the third trimester (n = 23)*[a] [42] *Breakthrough seizures occurred in 40% of the pregnancies in WWE who were seizure free prior to pregnancy (n = 23)*[a] [42] *Decline of ZNS C/D ratio by 35–36% has been associated with an increase in seizure frequency; however, the study was not designed to investigate seizure control and C/D fell even more in some pregnancies without seizures (n = 23)*[a] [42]	*More research on ZNS during pregnancy is needed. Because of limited and insufficient evidence of pharmacokinetics during pregnancy, monitoring of ZNS during pregnancy is advised when clinical features deteriorate or the risk on seizure occurrence is increased* *Practical advice* Before conception: measure the total ZNS serum trough concentration two times if the patient is on stable seizure control with a minimal dose to determine the RC During pregnancy: measure the total ZNS serum trough concentration when decided necessary and maintain the RC by adjustment of the dose After delivery: measure the total ZNS serum trough concentration and adjust the dose gradually over 0–21 days after delivery depending on the previous concentration and adverse drug reactions until stable. Postpartum monitoring is not required when the AED dose has not changed during pregnancy

New information and recommendations were formulated if possible and displayed in italics

CBZ carbamazepine, *CBZ-EPO* carbamazepine-epoxide, *C/D ratio* concentration/dose ratio, *CLB* clobazam, *dmCLB N*-desmethylclobazam, *GBP* gabapentin, *LCM* lacosamide, *LEV* levetiracetam, *LTG* lamotrigine, *LIC* licarbazepine, *OC* oral contraceptive, *OXC* oxcarbazepine, *PER* perampanel, *RC* reference concentration, *TPM* topiramate, *VPA* valproate, *ZNS* zonisamide

[a]Polytherapies were included

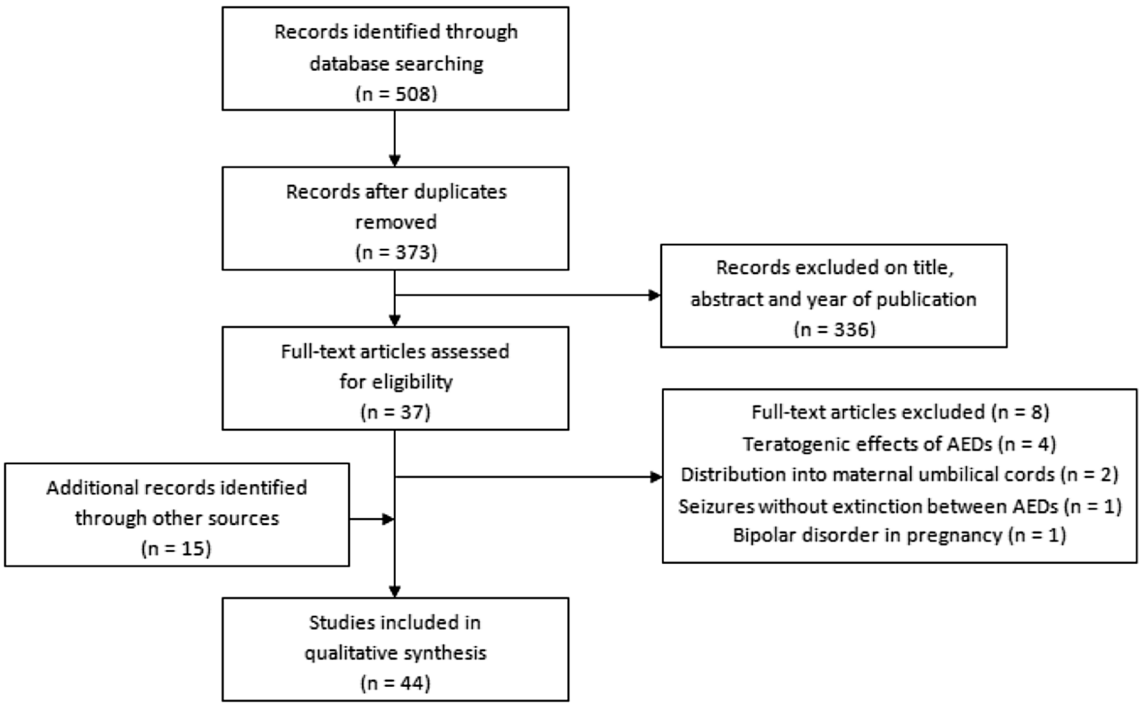

Fig. 1 Flow-chart of literature search

decreased gradually throughout pregnancy [38], owing to an increased clearance probably by enhanced hepatic metabolism [25, 27, 30, 32]. It was therefore suggested that seizure deterioration could be caused by the changed LIC plasma concentration [27, 38]. The postpartum elimination returned to normal within the first 4–8 weeks after delivery [38].

3.6 Topiramate

Seizure frequency increased in 47% of the TPM pregnancies (including polytherapy) during the second and third trimesters according to one study [39]. In 27% of those pregnancies, seizure frequency also increased in the first trimester [39]. In the remaining pregnancies, patients were either seizure free before and during pregnancy or the seizure frequency remained stable during pregnancy [39]. As a consequence, high rates of dose increase or the addition of another AED were observed during the second and third trimesters [39]. Topiramate serum concentrations decreased throughout pregnancy and showed a maximum decline during the second and third trimesters [19, 39, 40]. One study presumed an increased clearance of TPM as a result of an increase in renal blood flow and a decrease in tubular reabsorption [19]. Results on the distribution and metabolism of TPM during pregnancy were conflicting between the different studies and evidence on postpartum elimination was lacking.

3.7 Valproate

Seizures occurred in 25–40% of the VPA pregnancies (including polytherapy) according to the reviewed studies [17, 41]. One study reports an increased seizure occurrence on VPA monotherapy during the second and third trimesters compared with the first trimester [17]. Comparison of seizure frequencies before pregnancy and during pregnancy has not been described yet. Dose adjustments were not often performed during VPA pregnancies, only in 7% [17]. Furthermore, unbound VPA fraction was found to be highly variable [41] and the effect of pregnancy on VPA clearance was not studied.

3.8 Zonisamide

An increase in seizures was reported in 33% of the ZNS pregnancies, which especially occurred in the second and third trimesters [42]. In addition, breakthrough seizures occurred in 40% of the pregnancies (including polytherapy) in WWE who were seizure free in the pre-pregnancy year [42] and dose adjustments were frequently performed during pregnancy [42]. More data on seizure frequency compared with pre-pregnancy seizure frequency are lacking. Several studies report an increased ZNS clearance and a decreased ZNS plasma concentration during pregnancy [16, 42, 43]. The decline of ZNS concentration is probably associated

with the observed increase of seizure frequency [42]. Evidence for changed clearance after pregnancy was lacking.

3.9 Gabapentin, Lacosamide, and Perampanel

To our knowledge, there are no data on the pharmacokinetics, seizure frequency, or dose adjustments of GBP, LCM, and PER during and after pregnancy.

4 Clinical Implications

Although the evaluation of the safety of AED use during pregnancy has received much scientific attention over the last few years [1, 7, 8, 12], knowledge about the pharmacokinetics and its influence on seizure frequency is still scarce. An important reason may be the reluctance to study new drugs in pregnant women because of their unknown risks for teratogenic effects. Nevertheless, new information about the pharmacokinetics of AEDs during pregnancy based on prospective studies and case reports in pregnant WWE has become available, leading to this update of the practice parameter update of Harden et al. [3] of the AAN and AES.

4.1 Pregnancy-Related Changes

A general recommendation for AED use during pregnancy is to prescribe AEDs at the lowest effective dose. In addition, monotherapy is preferred above polytherapy and TDM-guided dosing is recommended for some AEDs. However, drug-specific recommendations can only be made if the drug-specific pharmacokinetic changes during pregnancy are clear and when these changes are associated with an increased risk of seizures. Increased plasma volume may lead to an increased volume of distribution, which potentially reduces the AED concentration [5, 44]. It is suggested that circulating pregnancy hormones could compete with highly protein-bound AEDs for protein binding. Furthermore, the serum albumin level may also be reduced as a result of the increased plasma volume. These pregnancy-related changes could increase the unbound (pharmacologically active) fraction and affect the clearance of (especially highly) protein-bound AEDs. Pregnancy-related increased renal blood flow and glomerular filtration rate may reduce the serum concentrations of AEDs eliminated through the kidneys [44]. In addition, activities of some cytochrome P450 and uridine diphosphate glucuronosyltransferase isoenzymes are induced during pregnancy, which may lead to increased metabolism of AEDs predominantly metabolized by these isoenzymes. We have searched for evidence in the literature for drug-specific pharmacokinetic changes during pregnancy, which is presented in Table 1 and described per AED.

4.2 Determine the Reference Concentration Before Pregnancy

According to the reviewed studies, it is generally recommended to determine the trough RC of AEDs before conception when the WWE are on stable seizure control on the lowest effective AED dose and to maintain this AED concentration throughout pregnancy by adjusting the dose. However, determining of the RC before conception is not always performed in practice (especially when a pregnancy is unplanned). Hence, we emphasize the importance of determining the individual RC during stable seizure control for every AED before conception. We recommend to measure trough concentrations (for total and/or unbound concentration, see Table 2) two times before conception to take intra-individual differences into account. We also recommend measuring total and unbound AEDs trough concentrations when the AED is highly protein bound ($\geq 90\%$) and to measure only total serum trough concentrations when the AED is not highly protein bound ($< 90\%$).

Furthermore, it is important to know that plasma concentrations of some AEDs can be influenced by discontinuing estrogen-containing OCs [22, 23]. Use of these OCs in combination with LTG is associated with a reduction in the LTG concentration by approximately 50% [22, 23]. Estrogen-induced hepatic glucuronidation has been implicated in the decline of LTG concentrations [22, 23]. Hence, when WWE have been using OCs before planning pregnancy, the LTG concentration will rise strongly after discontinuing the OCs [45]. Based on this knowledge, we recommend to measure the LTG concentration twice and determine the RC on continuous use of the OC. Thereafter, we advise to reduce the LTG dose by 50% at the same time of discontinuing the OC to maintain the RC. Within 1 week to 1 month after discontinuing the OC, we advise monitoring a third trough LTG concentration to determine if the LTG concentration is comparable with the previous RC. Repeated monitoring and adjustment of the LTG dose could be necessary to titrate the WWE on stable seizure control before conception. Other AEDs with a major elimination pathway through glucuronidation, such as OXC's metabolite LIC (50–60%) and VPA (30–50%) [14], are also likely to show a decrease in concentration because of the influence of OCs, which should be taken into account by measuring the RC. However, for LIC and VPA, this effect is of less importance compared with LTG, which is almost fully eliminated through glucuronidation [46]. No evidence has been reported yet for a possible influence of discontinuing the OC on the pharmacokinetics of other AEDs. Nevertheless, there is a possibility that changing hormone levels may have some influence on the AED concentration. Because we assume the WWE will be on stable seizure control 1 month after discontinuation of the OC, we advise to determine the RC 1 month after

discontinuing the OC and before conception. The importance of determining the RC and the different strategies for determining the RC when the WWE used OCs underlines the need for intensive pre-pregnant guidance of the WWE by clinicians.

4.3 Monitoring and Dose Adjustment During Pregnancy

For WWE receiving AED treatment without routine TDM advice during pregnancy, clinicians should decide when TDM could be of value in treating WWE receiving AED treatment during pregnancy. Therefore, clinical features should be taken into account. Therapeutic drug monitoring of those AEDs could be helpful when clinical features deteriorate. Nevertheless, the EMPiRE study from Thangaratinam et al. [47] claims that there is no evidence to suggest that TDM-guided dosing of AEDs in pregnancy improves seizure control compared with dosing guided by clinical effects. One inclusion criterion in this study was 'viable pregnancy of < 24 weeks gestation', which means that they could not compare AED concentrations during pregnancy with pre-pregnancy concentrations for every included patient. As a result, the often sharp fall of LTG concentration and possibly other AEDs in the beginning of pregnancy could have been missed, which misleads the conclusion. In our view and using this knowledge, TDM can be very helpful in providing clinicians guidance to avoid seizures during pregnancy.

After deciding TDM could be beneficial for the improvement of the individual AED therapy, trough AED concentrations should be compared with the pre-pregnancy RCs. Based on the results, clinicians have to decide if a dose adjustment is required. Many reviewed studies recommend a dose adjustment during pregnancy. However, clear advice when to perform a dose adjustment is lacking.

Therefore, we have formulated a guide on when to perform dose adjustments of AEDs during pregnancy, which can be considered by clinicians when WWE are pregnant. This guidance is based on two sources of drug variation allowed in practice: the variation between analytical results and the batch-to-batch variation in drug content. The variation between analytical results of drug concentrations in blood allowed by the US Food and Drug Administration [48] and the European Medicines Agency [49] amounts to 15%. Following that variation, we assume that deviations in AED concentrations less than 15% from the RC could be the result of the analysis and do not necessarily require dose adjustments. The actual amount of the active ingredient of a drug dispensed may vary from 90 to 110% of the amount declared on the label [50], which results in a maximum batch-to-batch variation of 20%. The total accepted variation of those variations together will be the maximum: $\sqrt{(20^2 + 15^2)} = 25\%$. Following this calculation, deviations in AEDs through concentrations between 15 and 25% from the RC are more likely to cause seizures or side effects. Therefore, we suggest to consider a dose adjustment in this range taking risk factors into account. For example, polytherapy of AEDs, type of seizures and, most important, seizure occurrence in the year prior to pregnancy are such risk factors [3, 16, 18, 24]. Seizure occurrence in the pre-pregnancy month is even associated with a 15 times higher risk of developing seizures during pregnancy [18]. In the case of WWE being seizure free during the year prior to pregnancy, we suggest that a dose adjustment is not necessary. Last, we advise a dose adjustment when the drug concentration decreases more than 25% from the RC to pursue the RC and avoid seizures. However, the risk on fetal exposure should always be taken into account.

Other expert opinions on adjusting AED doses during pregnancy are mostly based on the results of LTG pregnancies. Their approach is to adjust the AED dose when the AED concentration falls below 65% of the pre-pregnancy baseline concentration because it has been demonstrated that the seizure frequency of WWE on LTG pregnancies increased when this occurred [4, 26]. However, it has not been demonstrated that this also applies to other AEDs than LTG.

We agree that we have formulated a stricter regime of when to perform a dose adjustment of AEDs to protect the WWE and the unborn from seizures during pregnancy. However, our approach with the different deviation categories of 0–15%, 15–25%, and > 25% of the RC is similar to the Danish policy of pursuing the RC during pregnancy [51]. Future prospective research could use our systematic approach of when to perform TDM of AEDs during pregnancy. This allows future studies to acquire pharmacokinetic and pharmacotherapeutic knowledge in a structural manner.

4.4 Monitoring and Dose Adjustments after Delivery

The pharmacokinetics of AEDs will return to the pre-pregnancy situation after delivery. Therefore, dose adjustments performed during pregnancy could lead to an overdose and side effects after pregnancy. As the pharmacokinetics and clearance of AED can rapidly return to normal after birth, we have to consider a dose adjustment after delivery. Major changes in dose during pregnancy will request an almost immediate start of tapering the dose after delivery towards pre-pregnancy concentrations. Smaller adjustments in dose during pregnancy require minor and less frequent interventions. Therefore, we advise monitoring trough AED concentrations and gradually adjusting the dose over 0–21 days after delivery until normalization, when the AED dose was adjusted during pregnancy. Post-partum drug monitoring is

not required when the AED dose has not been changed during pregnancy. It is helpful to instruct the WWE that specific toxic symptoms of the used AED, such as diplopia, dizziness, and ataxia, can occur if the dose is not adjusted rapidly enough. In addition, we advise not to pursue pre-pregnancy values but concentrations that are slightly higher to provide the WWE with more seizure protection after delivery as the women may experience more stress and sleep deprivation.

4.5 Therapeutic Drug Monitoring of Specific Antiepileptic Drugs

Because of minimal changes in CBZ concentrations and clearances during pregnancy that appeared not to be related with increased seizure frequency, TDM of CBZ was suggested as unnecessary during pregnancy. However, the sample sizes of the reviewed studies are small, which necessitates future larger studies for confirmation of this suggestion. Based on the literature, TDM of CBZ currently seems not useful or profitable for WWE, as concentrations cannot be related to seizure occurrence. Therefore, we suggest to determine only the total trough RC of CBZ and CBZ-epoxide before pregnancy for comparison purposes. A change of CBZ treatment should depend on clinical signs, seizure risks, and previous doses until more evidence on CBZ is obtained in larger studies.

The reviewed studies of LTG and LEV pregnancies conclude that seizure deterioration is a consequence of a decline in concentrations of LTG and LEV, respectively. Although many of the reviewed LEV studies included patients receiving AED polytherapy, it is expected that the pharmacokinetics of LEV does not change as a result of polytherapy because LEV has a low protein binding and few drug–drug interactions. Hence, we can use the pharmacokinetics of LEV during polytherapy as a reference to discuss the changed LEV concentrations. Therefore, seizure occurrence of WWE treated with LTG or LEV during pregnancy might be controlled by routine monitoring of the total LTG or LEV concentrations and dose adjustments. Hence, we advise for these pregnancies to measure the total serum RC of LTG and LEV twice before conception, monthly during pregnancy, and after delivery until stable seizure control is obtained with gradual dose adjustments over 0–21 days. Dose adjustments of LTG and LEV could be necessary during and after pregnancy depending on the clinical features, seizure risk factors, adverse drug reactions, and previous dose. When the WWE are not on stable seizure control with twice-daily LEV immediate-release tablets, it can be considered to divide the daily dose over three of four times a day or change to slow-release tablets if available. Because of the short half-life of LEV, especially during pregnancy, slow-release LEV tablets have preference, if available.

Seizure deterioration during OXC pregnancy has been associated with decreased total LIC trough concentrations [38], which reinforces TDM before, during, and after pregnancy. However, one patient experienced an increase in the seizure frequency of more than 50% despite a 6% increase in LIC plasma concentration, which suggests other factors than plasma concentrations may contribute to seizure deterioration [38]. Support for this finding is limited and more research on OXC use during pregnancy is needed. Considering this, we advise a TDM regime with necessary dose adjustments before, during, and after pregnancy comparable to LTG and LEV pregnancies.

According to a recent study TPM (one of the newer AEDs), clearance is significantly increased during the second and third trimesters of pregnancy resulting in lower drug concentrations [4]. This is presumably caused by a pregnancy-related increased renal blood flow and decreased tubular reabsorption because TPM is excreted unchanged by the kidneys [19]. To our knowledge, the study of Voinescu et al. [4] is the first study to confirm the relationship between the decreased TPM concentrations and increased seizure frequency [4]. Based on this study, we recommend a TDM regime of before, during, and after pregnancy comparable with LTG, LEV, and OXC pregnancies.

There is strong evidence that VPA use during pregnancy is associated with an increased risk on congenital malformations. Therefore, the International League Against Epilepsy, European Academy of Neurology and the European Medicines Agency [52] have recently recommended that VPA should preferably be avoided during pregnancy [53]. However, several studies have found that the teratogenic risk of VPA is dose dependent and recommend not to prescribe VPA at doses exceeding 500–600 mg/day in fertile women. Continuing the administration of VPA during pregnancy can only be considered for women who are well controlled on a low dose of VPA 500–600 mg/day with no other alternatives being available [10, 53, 54]. Furthermore, it is suggested that the unbound VPA concentration increases as result of a decrease in serum albumin during pregnancy, when at the same time, the total VPA concentration will decrease [41]. However, WWE and partners must be very clearly informed of the teratogenic risks and possible long-term effects on the child. Therefore, when it is decided to continue VPA during pregnancy, we advise TDM of total and unbound VPA concentrations in the same schedule as LTG, LEV, and OXC pregnancies. In addition, it could be considered to divide the daily dose of sustained-release VPA over three or four times a day to reduce the teratogenic risk as a result of high peak concentrations.

Data on the pharmacokinetics and sufficient data on seizure occurrence during pregnancy are lacking for WWE treated with CLB, GBP, LCM, and PER during pregnancy. This is mainly owing to the lack of teratogenic safety data,

which have resulted in the limited use of these AEDs in pregnant women. Therefore, guidelines for performing TDM during pregnancy are lacking for these AEDs. There is some evidence of an increased clearance and decreased serum concentration of ZNS during pregnancy. However, the study included pregnancies on the polytherapy of ZNS with other AEDs, which makes it difficult to rule out the effects of the other drugs on ZNS [32]. Therefore, more research on these AEDs during pregnancy is needed. Hence, we recommend caution when prescribing one of these AEDs during pregnancy and the monitoring of trough concentrations (total concentrations of GBP, LCM, and ZNS and total and unbound concentrations of CLB, dmCLB, and PER due to strong protein binding [55]) twice before conception to determine the RC and guide the dose adjustment of those AEDs during pregnancy when the patient deteriorates or the risk for seizure occurrence has increased.

4.6 Further Research

Although much is already known about the pharmacokinetics of some AEDs during pregnancy, more research on the pharmacokinetic changes of some other AEDs during pregnancy is needed. In particular, data on the pharmacokinetics of CLB, GBP, LCM, PER, and ZNS during pregnancy are not available. Moreover, the relationship between the pharmacokinetic changes of AEDs and changes in seizure frequency should be investigated more precisely and perhaps result in physiology-based population pharmacokinetic models in pregnant women. In addition, for some AEDs, only polytherapy data are available, which confounds the 'drug-specific' effect on seizure frequency and the effect of pregnancy on drug pharmacokinetics. This reinforces the need for research on AED monotherapies. Furthermore, factors other than drug plasma concentrations may contribute to seizure deterioration as suggested in one OXC case report [38], which encourages more research on seizure protection during pregnancy.

5 Conclusions

This review has added new insights into the pharmacokinetic changes of AEDs and seizure frequency and provides guidance on the monitoring and management of AEDs during pregnancy. We advise to measure RCs of all AEDs twice before conception. The recommendations on TDM of AEDs during pregnancy can be divided into those that are recommended to routinely measure, which include LEV, LIC, LTG, TPM and VPA if avoiding use during pregnancy is impossible. Monitoring during pregnancy should be considered in CLB, GBP, LCM, PER, and ZNS pregnancies depending on clinical features and seizure-predicting factors. The role of TDM is questionable during CBZ pregnancies. We advise considering dose adjustments of AEDs during pregnancy when the AED concentration decreases between 15 and 25% from the pre-pregnancy RC in combination with risk factors. Seizure occurrence in the pre-pregnancy year is the most important seizure-predicting factor during pregnancy. We advise dose adjustment if the AED concentration decreases more than 25% from the RC, and postpartum monitoring only when the AED dose was changed during pregnancy. Although new information on AED pharmacokinetics during pregnancy has become available, more research on TDM of AED use during pregnancy is still needed.

Compliance with Ethical Standards

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