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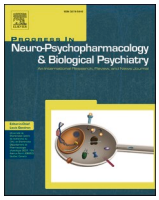

The impact of pregnancy on the pharmacokinetics of antiseizure medications: A systematic review and meta-analysis of data from 674 pregnancies

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ABSTRACT

Objective: Increasing evidence suggests that the physiological changes of pregnancy may impact pharmacokinetics of antiseizure medications (ASM), and this may affect treatment outcomes. The aim of this study was to quantify the pregnancy impact on the ASM pharmacokinetics.

Methods: A systematic literature search was conducted in PubMed/EMBASE in November 2022 and updated in August 2023 for studies comparing levels of ASM in the same individuals during pregnancy and in the preconception/postpartum period. Alteration ratios between the 3rd trimester and baseline were estimated. We also performed a random-effects meta-analysis calculating between-timepoint differences in mean differences (MDs) and 95% confidence intervals (95%CIs) for dose-adjusted plasma concentrations (C/D ratios). Study quality was assessed using the ClinPK guidelines.

Results: A total of 65 studies investigating 15 ASMs in 674 pregnancies were included. The largest differences were reported for lamotrigine, oxcarbazepine and levetiracetam (alteration ratio 0.42, range 0.07–2.45, 0.42, range 0.08–0.82 and 0.52, range 0.04–2.77 respectively): accordingly, C/D levels were lower in the 3rd trimester for lamotrigine, levetiracetam and the main oxcarbazepine metabolite monohydroxycarbazepine (MD = -12.33 $\times 10^{-3}$, 95%CI = -16.08 to -8.58×10^{-3} (μg/mL)/(mg/day), $p < 0.001$, MD = -7.16 (μg/mL)/(mg/day), 95%CI = -9.96 to −4.36, p < 0.001, and MD = -4.87 (μg/mL)/(mg/day), 95%CI = -9.39 to −0.35, $p = 0.035$, respectively), but not for oxcarbazepine (MD = 1.16×10^{-3} (μg/mL)/(mg/day), 95%CI = -2.55 to 0.24×10^{-3}, $p = 0.10$). The quality of studies was acceptable with an average rating score of 11.5.

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Conclusions: Data for lamotrigine, oxcarbazepine (and monohydroxycarbazepine) and levetiracetam demonstrate major changes in pharmacokinetics during pregnancy, suggesting the importance of therapeutic drug monitoring to assist clinicians in optimizing treatment outcomes.

1. Introduction

Pregnancy is characterized by numerous physiological changes across various organ systems (Westin et al., 2018a), many of which impact absorption, distribution, metabolism and excretion of medications (Pariente et al., 2016). In fact, it is the complex interplay of the simultaneous alterations of several factors including the degree of protein binding, volume of distribution, liver cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzyme activities, efflux transporter capacities and renal function (Deligiannidis et al., 2014) that result in what is measured as a blood concentration or level. Given so many underlying contributors, it is challenging to precisely predict the impact of pregnancy on the disposition of a medication. Ultimately, the metabolic pathway of each medication may be the most decisive in the context of pregnancy impact on drug disposition (Westin et al., 2018a; Westin, 2018). For instance, for hepatically-metabolized medications, patterns of alterations strongly depend on activity changes of the implicated CYP isoenzymes; specifically, activity changes vary in magnitude, but also in direction, i.e. decrease or increase (Westin et al., 2018a). Such alterations invariably progress throughout pregnancy and display a peak in the 3rd trimester (Pariente et al., 2016), where the largest changes in terms of drug disposition compared to preconception are expected (Westin et al., 2017). However, the clearance of medications that are renally excreted is also expected to increase up to 50% during pregnancy following changes of renal function throughout gestation (Westin et al., 2018a).

Antiseizure medications are among the most prescribed medications in pregnant women (Werler et al., 2023). Evidence of pregnancy effects on pharmacokinetics of antiseizure medications has accumulated over the years (Mygind et al., 1976; Tomson et al., 2019; Harden et al., 2009). These effects have been linked to dose changes, which are required in order to offset alterations in drug disposition and to maintain seizure control (or another therapeutic effect depending on the treatment indication) during pregnancy (Sit et al., 2008; Wisner et al., 1993). Within this realm, the assessment of blood (plasma or serum) levels of antiseizure medications, also known as therapeutic drug monitoring (TDM), comprise a routine clinical tool that enables individualized dosing adjustment during pregnancy based on regular assessments of drug disposition changes (Deligiannidis et al., 2014; Westin, 2018). Indeed, regular TDM is suggested as integral part of peripartum prescription of antiseizure medications by several guidelines (Tomson et al., 2019; Harden et al., 2009). However, a comprehensive up-to-date overview including quantification of the impact of pregnancy on pharmacokinetics of antiseizure medications is needed to inform clinical decision algorithms.

The aim of this study was to conduct a systematic review and meta-analysis of studies assessing plasma or serum concentrations of antiseizure medications in the 3rd trimester of pregnancy and either the preconception or postpartum period, in order to quantify the pregnancy effects on drug disposition and ultimately inform dosing algorithms.

2. Methods

We conducted our study according to the PRISMA guidelines (Hutton et al., 2015) and it was registered with PROSPERO (reg. number CRD42020181839). Two researchers (NK and CTS) independently searched for studies assessing concentrations of antiseizure medications in maternal blood (serum or plasma), in the 3rd trimester and before or >4 weeks after pregnancy in PubMed and EMBASE databases with the following search strategy: (antiepileptic OR "mood stabilizer" OR anticonvulsant OR barbexaclone OR brivaracetam OR carbamazepine OR cenobamate OR "chloral hydrate" OR clobazam OR clonazepam OR diphenylhydantoin OR divalproex OR divalproate OR erlosamide OR eslicarbazepine OR ethosuximide OR ethadione OR etiracetam OR felbamate OR gabapentin OR mesuximide OR metharbital OR lacosamide OR lamotrigine OR levetiracetam OR oxcarbazepine OR perampanel OR phenobarbital OR phenytoin OR pregabalin OR primidone OR rufinamide OR topiramate OR valproate OR "valproic acid" OR vigabatrin OR zonisamide) AND (blood OR serum OR plasma) AND (postnat* OR lactat* OR pregnan* OR antepart* OR postpart*). Databases were searched in November 2022 for articles since data inception and updated in August 2023. An additional search in PsychINFO and Cochrane libraries did not yield any further studies. We additionally scrutinized references from identified works for reports of interest that may have been missed with the systematic search.

2.1. Inclusion & exclusion criteria

Studies with a within-subject study design, with multiple measures of antiseizure medications' levels in plasma or serum (hereafter referred to as "plasma" for the purposes of this manuscript) during and outside (before or after) pregnancy, referred to as "baseline" were included. We only included studies with assessments during pregnancy obtained in the 3rd trimester (≥gestational week 26), where the largest changes may be expected. We included baseline samples when assessed before pregnancy or more than four weeks following delivery, which reflects a time frame after which the impact of pregnancy-related physiological alterations on drug pharmacokinetics is unlikely to be sustained (Stika et al., 2022). The study did not exclude any diagnoses and included any total daily dosage of antiseizure medications. As plasma samples taken for clinical TDM are typically obtained at trough conditions, we did not use any restrictions regarding how this was defined in the studies (i.e. minimum/maximum number of hours between last drug intake and blood sampling). We considered total levels of antiseizure medications. Animal studies were excluded.

2.2. Data extraction

Two authors (NK and CTS) independently extracted data including number of pregnancies, total daily doses of antiseizure medications, concentrations of antiseizure medications (means and ranges or standard deviations) in maternal plasma in the 3rd trimester, and in the preconception or postpartum periods (specified by the number of weeks at postpartum). When multiple measurements were taken per patient in the 3rd trimester or at baseline, we estimated mean values. When data were provided in nmol/L or μmol/L values were converted to ng/mL using molecular weight-based conversion factors (Hiemke et al., 2018). When studies estimated dose divided by concentration values as surrogates of drug disposition, we estimated the inverted values. When levels of antiseizure medications were reported below the limit of quantification (LOQ), we used the LOQ value in our estimations (Paulzen et al., 2019). When additional information was required to interpret data, the original authors were contacted.

2.3. Outcomes & statistical analyses

The primary outcome of our analysis was the "alteration ratio", defined as the ratio of the dose-adjusted plasma concentration of the antiseizure medications in the 3rd trimester and the baseline dose-adjusted plasma concentrations (preconception and/or postpartum).

Practically, an alteration ratio < 1 indicates that the 3rd trimester dose-adjusted concentration is lower than baseline, and vice versa. Mean ratios from each study were pooled for the estimation of a combined alteration ratio; ratios of individual patients were pooled as in an individual participant data meta-analysis. We exclusively used means of ratios instead of ratios of means as we aimed to intraindividually investigate alteration patterns. On the occasion that cohort information was available rather than individual patient data, we estimated combined ratios by weighting the alteration ratio of each study by the study's sample size building upon the theoretical framework underlying previous secondary analyses of TDM data (Schoretsanitis et al., 2017; Schoretsanitis et al., 2018a; Schoretsanitis et al., 2018b; Schoretsanitis et al., 2019).

We performed a subgroup analysis estimating alteration ratios in women with antiseizure monotherapy or with concomitant use of pharmacokinetically non-interacting antiseizure medications only versus women with concomitant use of antiseizure medications with inducing properties throughout pregnancy, excluding patients with missing information on type (or lack) of co-medications. This subgroup analysis was deemed necessary given the frequency of combinations of antiseizure medications (Baftiu et al., 2018) and the inducing properties of carbamazepine, phenytoin, phenobarbital and primidone (Hiemke et al., 2018). Patients concomitantly prescribed valproate were not considered in any subgroup given valproate's partially unclear interaction potential with both, inducing and inhibiting properties (McGrane et al., 2022; Bennett and Shad, 2021; Tomson et al., 2006).

Complementarily, we applied a classical meta-analysis to estimate mean differences for alterations in dose-adjusted concentrations (ng/mL per mg/day) of antiseizure medications between 3rd trimester and baseline. Given the expected heterogeneity related to analytical methods, the inherently large variability of the TDM variables, but also the patient populations, we applied a random-effects model. Results were summarized using mean differences and 95% confidence intervals (95%CIs). The DerSimonian-Laird estimator was used to calculate the heterogeneity variance parameter (τ^2) (DerSimonian and Laird, 1986). Further, we calculated the I-square (I^2) statistic that indicates the proportion of variability potentially attributed to heterogeneity. Analyses were performed with the `meta` package in R (Schwarzer et al., 2015). We only performed meta-analyses when data from a minimum of three studies regardless of number of patients were available. Moreover, when estimates provided by authors used total daily doses per body weight (mg/kg), we did not include them in the meta-analyses.

2.4. Quality assessment

The methodological quality of the included studies was assessed using the ClinPK guidelines (Kanji et al., 2015).

3. Results

The search yielded 3890 references from Medline and 5951 from Embase. An additional search in PsychInfo and Cinhail did not report any further studies of interest. After removing 1374 duplicates, 8468 studies remained. After exclusion of 8239 records based on title and abstract review, 229 articles were full-text screened. 101 papers were excluded due to lack of TDM at both timepoints of interest, 24 reviews or comments, 12 papers not focusing on pharmacokinetic aspects, ten duplicates, eight papers with data not in a meta-analyzable form, five papers with unequal numbers of patients at the timepoints of interest, one animal study, one paper due to lack of data on daily dosages, one paper assessing saliva and not blood concentrations and one paper not possible to retrieve (Supplementary Fig. 1). Table 1 contains all relevant data from the 65 studies with 674 pregnancies finally included. The included studies covered a total of 15 antiseizure medications: brivatacetam (k = 1 study, $n = 2$ patients), carbamazepine (k = 10, $n = 116$), clonazepam (k = 2, $n = 7$), ethosuximide (k = 4, $n = 10$), lacosamide (k = 4, $n = 6$), lamotrigine (k = 27, $n = 276$), levetiracetam (k = 12, $n = 109$), oxcarbazepine (k = 4, $n = 25$) and monohydroxycarbazepine (k = 4, n = 25), perampanel (k = 1, n = 1), phenobarbital (k = 6, $n = 39$), phenytoin (k = 15, $n = 135$), primidone (k = 3, $n = 4$), topiramate (k = 4, n = 25), valproate (k = 7, $n = 19$) and zonisamide (k = 3, $n = 20$).

3.1. Brivaracetam

Alteration ratios were estimated in two patients from one study (Landmark et al., 2021) yielding a mean value of 0.85 ± 0.26, implying a reduction in 3rd trimester dose-adjusted brivaracetam levels to 85% of the preconception/postpartum values (Table 1). No subgroup analysis stratifying for concomitant use of antiseizure medications with inducing properties was performed, as no data from women with concomitant antiseizure medications with inducing properties was available.

3.2. Carbamazepine

Alteration ratios for carbamazepine in 10 cohorts (n = 116) ranged between 0.08 and 2.19 (Table 1) and the combined ratio was 0.90. Combined alteration ratios were 0.98 (0.50–1.65, $n = 8$, k = 5) and 0.97 (0.76–2.19, $n = 19$, k = 5) in women with vs. without concomitant use of antiseizure medications with inducing properties. We estimated a mean difference between 3rd trimester and baseline of -3.20×10^{-3} μg/mL per mg/day, 95%CI: -4.15 to -2.26×10^{-3}, $p < 0.001$ in the random-effects model of the meta-analysis; C/D levels were lower in the 3rd trimester (Fig. 1a). Observed heterogeneity was substantial ($I^2 = 100\%$, $p < 0.001$).

3.3. Clonazepam

Evidence for clonazepam derived from two cohorts ($n = 7$) with alteration ratios ranging between 0.85 and 1.18 and a combined alteration ratio of 0.90 (Kriel and Cloyd, 1982; Torbjörn et al., 1990). No subgroup analysis stratifying for concomitant use of antiseizure medications with inducing properties was performed, as no data from women with concomitant antiseizure medications with inducing properties was available.

3.4. Ethosuximide

Alteration ratios for ethosuximide in four cohorts ($n = 10$) ranged between 0.66 and 1.00 and the combined ratio was 0.86 (Table 1). Combined alteration ratios were 0.83 (0.66–1.00, $n = 2$, k = 1) and 0.70 (n = 1, k = 1) in women with vs. without concomitant use of antiseizure medications with inducing properties. In the meta-analysis we estimated a mean difference between 3rd trimester and baseline of −6.44 μg/mL per mg/day, 95%CI: −15.92 to 3.04, $p = 0.18$; C/D levels were lower in the 3rd trimester (Fig. 1b). Observed heterogeneity was minimal ($I^2 = 0\%$, $p = 0.99$).

3.5. Lacosamide

Evidence for lacosamide derived from four cohorts ($n = 6$); alteration ratios ranged between 0.73 and 1.28 with a combined alteration ratio of 0.91. Combined alteration ratios were 0.86 (n = 1, k = 1) and 0.83 (0.73–0.91, $n = 4$, k = 2) in women with vs. without concomitant use of antiseizure medications with inducing properties. In the meta-analysis we reported a mean difference between 3rd trimester and baseline of -4.55×10^{-3} μg/mL per mg/day, 95%CI: -8.04 to -1.05×10^{-3}, $p = 0.011$; C/D levels were lower in the 3rd trimester (Fig. 1c). Observed heterogeneity was substantial ($I^2 = 100\%$, $p < 0.001$).

3.6. Lamotrigine

Evidence for lamotrigine derived from 27 cohorts ($n = 276$); one

Table 1
Dose-adjusted blood levels, age, monotherapy, alteration ratios (pregnant state values divided by non-pregnant state values) for each cohort and combined alteration ratios for dose-adjusted levels of antiseizure medications. Numbers in parentheses refer to ranges. When dose-adjusted blood levels were not provided by the original authors, we calculated them.

Antiseizure medication	n	Age (years)	Monotherapy[a] (n)	3rd trimester	Baseline (pooled preconception & postpartum)	Alteration ratio	Combined alteration ratio	Quality	Reference
Brivaracetam	2	28.5 ± 5.0	2	$6.2 \pm 1.2 \times 10^{-3}$	$7.4 \pm 0.9 \times 10^{-3}$	0.85 ± 0.26	NA	9	Landmark 2021
	1	24.0	0	2.9×10^{-3}	5.9×10^{-3}	0.49		10	Lander 1977
	3	23.7 ± 4.5	1	$9.5 (6.1–14.7) \times 10^{-3}$	$12.8 (11.1–15.6) \times 10^{-3}$	0.72 ± 0.21		13	Dam 1979
	1	24.0	0	4.0×10^{-3}	8.0×10^{-3}	0.50		5	Niebyl 1979
	7	NP	NP	$3.7 \pm 15.0 \times 10^{-3}$	$7.5 \pm 24.0 \times 10^{-3}$	0.49		9	Lander 1981
	2	27.9 ± 3.8	NP	$8.5 \pm 4.1 \times 10^{-3}$	$11.7 \pm 7.4 \times 10^{-3}$	0.78 ± 0.20		12	Battino 1985
Carbamazepine	5	29.0 (23.0–32.0)	5	$8.3 \pm 28.9 \times 10^{-3}$	$10.8 \pm 32.6 \times 10^{-3}$	0.76	0.90 (0.08–2.19)	15	Yerby 1985
	6	NP	6	$568.18 \pm 2080 \times 10^{-3}$	636.943030×10^{-3}	0.89		12	Reisinger 2013
	22	NP	NP	282.3×10^{-3}	315.8×10^{-3}	0.89		9	Yerby 1990
	50	NP	NP	$7.2 \pm 15.0 \times 10^{-3}$	$7.3 \pm 15.0 \times 10^{-3}$	0.98		14	Tomson 1994a
	8	31.8 ± 5.7	5	$7.7 \pm 3.2 \times 10^{-3}$	$8.7 \pm 3.6 \times 10^{-3}$	01.02 ± 0.19		13	Bernus 1995
	4	31.2 ± 2.6	2	$12.4 \pm 8.8 \times 10^{-3}$	$9.2 \pm 4.3 \times 10^{-3}$	1.31 ± 0.61		12	Iwasaki 2016
Clonazepam	1	17.0	NP	11.63	9.81	1.18	0.90 (0.85–1.18)	6	Kriel 1982
	6	NP	NP	10.06 ± 17.60	11.81 ± 17.56	0.85		14	Tomson 1990
	2	NP	NP	32.26	45.45	0.71		9	Lander 1981
Ethosuximide	5	NP	NP	78.69 ± 306.38	82.28 ± 369.23	0.96	0.86 (0.66–1.00)	14	Tomson 1990
	2	30.0 ± 2.8	0	29.56 ± 6.22	36.01 ± 2.85	0.83 ± 0.24		12	Tomson 1994b
	1	NP	1	2.27	3.22	0.70		12	Reisinger 2013
	1	27.0	NP	37.03×10^{-3}	28.87×10^{-3}	1.28		2	Zárubová 2016
	1	23.0	0	21.40×10^{-3}	24.95	0.86		7	Fukushima 2021
	1	32.0	1	19.74×10^{-3}	21.62×10^{-3}	0.91		9	Landmark 2021
Lacosamide	3	26.4 (18.0–38.0)	3	$21.22 \pm 10.46 \times 10^{-3}$	$26.19 \pm 11.28 \times 10^{-3}$	0.80 ± 0.06	0.91 (0.73–1.28)	12	Zutshi 2021
	1	24.0	0	8.40×10^{-3}	25.0×10^{-3}	0.34		11	Rambeck 1997
	1	25.0	1	2.82×10^{-3}	16.41×10^{-3}	0.17		10	Tomson 1997
	8	28.4 ± 6.8	5	$7.79 \pm 6.55 \times 10^{-3}$	$15.20 \pm 10.84 \times 10^{-3}$	0.63 ± 0.47		14	Ohman 2000
	8	27.6 ± 2.3	2	$586.83 \pm 211.58 \times 10^{-3b}$	$873.43 \pm 449.81 \times 10^{-3b}$	0.78 ± 0.41		15	Tran 2002
	16	29.3 ± 4.6	16	$4.42 \pm 1.23 \times 10^{-3}$	$17.94 \pm 4.96 \times 10^{-3}$	0.26 ± 0.08		15	Öhman 2008
	3	31.5 (23.0–37.0)	3	$7.28 \pm 2.44 \times 10^{-3}$	$22.27 \pm 7.04 \times 10^{-3}$	0.33 ± 0.04		16	Fotopoulou 2009
	1	27.0	0	30.75×10^{-3}	38.0×10^{-3}	0.81		10	Kacirova 2010
	3	29.0 (26.0–33.0)	3	$399.84 \pm 81.81 \times 10^{-3}$	$1034.90 \pm 270.33 \times 10^{-3}$	0.39 ± 0.04		11	Liporace 2004
	1	NP	NP	18.25×10^{-3}	12.95×10^{-3}	1.41		2	Vajda 2006
	2	34.0 ± 1.4	2	$7.10 \pm 1.54 \times 10^{-3}$	$15.31 \pm 2.01 \times 10^{-3}$	0.46 ± 0.04		9	Wegner 2010
	18	26.8 (17.0–39.0)	18	$20.42 \pm 8.33 \times 10^{-3}$	$63.71 \pm 16.14 \times 10^{-3}$	0.33 ± 0.12		16	Reimers 2011
	4	29.0 ± 4.8	3	$8.17 \pm 2.11 \times 10^{-3}$	$20.58 \pm 14.20 \times 10^{-3}$	0.59 ± 0.43		13	Clark 2013
	69	NP	69	$478.47 \pm 990.0 \times 10^{-3b}$	$1149.42 \pm 2380.85 \times 10^{-3b}$	0.42		12	Reisinger 2013
	7	33.7 ± 4.4	6	$8.67 \pm 3.55 \times 10^{-3}$	$31.44 \pm 11.24 \times 10^{-3}$	0.30 ± 0.15		12	Iwasaki 2016
	6	31.4 ± 4.6	6	$17.01 \pm 8.25 \times 10^{-3}$	$24.47 \pm 15.67 \times 10^{-3}$	0.96 ± 0.66		10	Ohtani 2016
	1	30.0	0	540×10^{-3b}	220×10^{-3b}	2.45		5	Rumpel 2017
	99	31.0 (21.0–43.0)	99	$5.46 \pm 2.53 \times 10^{-3b}$	$15.20 \pm 5.71 \times 10^{-3b}$	0.36 ± 0.04		13	Petrenaite 2005
	10	27.6 ± 4.0	10	$9.77 \pm 4.04 \times 10^{-3b}$	$32.19 \pm 14.99 \times 10^{-3b}$	0.41 ± 0.29		12	Ding 2019
Lamotrigine	7	28.9 ± 3.8	7	$639.35 \pm 265.65 \times 10^{-3b}$	$1130.00 \pm 279.20 \times 10^{-3b}$	0.55 ± 0.17	0.42 (0.07–2.45)	13	Wang 2021

(*continued on next page*)

Table 1 (*continued*)

Antiseizure medication	n	Age (years)	Monotherapy[a] (n)	3rd trimester	Baseline (pooled preconception & postpartum)	Alteration ratio	Combined alteration ratio	Quality	Reference
	11	28.8 (23.0–35.0)	11	$5.83 \pm 2.86 \times 10^{-3}$	$20.83 \pm 10.80 \times 10^{-3}$	0.31 ± 0.10		14	Yin 2022
	5	NP	NP	0.50 ± 1.33	0.77 ± 1.75	0.65		5	Pennell 2005
	12	NP (21.0–37.0)	NP	0.002 ± 0.004	0.008 ± 0.017	0.29		16	Tomson 2007
	12	29.0 (21.0–38.0)	NP	3.74 ± 1.43	8.01 ± 4.03	0.55 ± 0.29		9	Westin 2008
	5	32.2 ± 4.5	5	6.84 ± 5.25	8.84 ± 2.01	0.72 ± 0.41		13	López-Fraile 2009
	15	NP	15	0.46 ± 0.90[b]	0.92 ± 3.33[b]	0.51		12	Reisinger 2013
	8	NP (23.0–36.0)	NP	0.37	0.6	0.62		4	Janousek 2013
	1	16.0	1	2.01	13.75	0.15		8	Garrity 2014
	8	30.7 ± 3.2	7	8.57 ± 4.51	18.69 ± 5.42	0.48 ± 0.26		12	Iwasaki 2016
	15	30.0 ± 4.0	15	5.31 ± 2.42	9.12 ± 3.17	0.69 ± 0.61		15	Berlin 2019
	7	30.2 (22.0–37.0)	7	4.83 ± 1.35	14.62 ± 4.30	0.36 ± 0.16		14	Yin 2022
Levetiracetam	21	30.8 (25.0–40.0)	NP	5.12 ± 2.97	12.73 ± 7.52	0.50 ± 0.35	0.52 (0.04–2.77)	13	Schelhaas 2022
	2	27 ± 8.5	2	$0.03 \pm 0.027 \times 10^{-3}$	$0.30 \pm 0.21 \times 10^{-3}$	0.10 ± 0.02		15	Mazzucchelli 2006
Oxcarbazepine	20	NP	20	$0.46 \pm 1.47 \times 10^{-3b}$	$1.10 \pm 4.35 \times 10^{-3b}$	0.42	0.42 (0.08–0.82)	12	Reisinger 2013
	1	NP	1	7.78×10^{-3}	9.44×10^{-3}	0.82		12	Zutshi 2021
	2	31.9 (29.0–34.0)	2	$5.49 \pm 0.81 \times 10^{-3}$	$11.13 \pm 4.80 \times 10^{-3}$	0.56 ± 0.31		14	Yin 2022
	7	NP	NP	$8.78 \pm 1.53 \times 10^{-3}$	$14.07 \pm 3.30 \times 10^{-3}$	0.63 ± 0.07		16	Christensen 2006
Mono-hydroxycarbazepine (MHD)	2	27 ± 8.5	2	$3.27 \pm 1.33 \times 10^{-3}$	$24.47 \pm 16.47 \times 10^{-3}$	0.20 ± 0.19	0.60 (0.06–0.87)	15	Mazzucchelli 2006
	14	28.1 (25.0–37.0)	14	$11.45 \pm 2.90 \times 10^{-3}$	$11.60 \pm 2.81 \times 10^{-3}$	1.02 ± 0.30		16	Petrenaite 2009
	2	34.0 ± 1.4	2	$5.35 \pm 0.44 \times 10^{-3}$	$13.11 \pm 2.35 \times 10^{-3}$	0.41 ± 0.04		9	Wegner 2010
Perampanel	1	32.0	1	65.56	40.21	1.63	NA	11	Landmark 2021
	13	NP	NP	0.22 ± 0.07	0.33 ± 0.1	0.75 ± 0.47		10	Mygind 1976
	2	25.0 ± 1.4	0	0.09 ± 0.006	0.16 ± 0.013	0.57 ± 0.08		10	Lander 1977
Phenobarbital	6	26.8 ± 2.9	3	0.19 ± 0.05	0.23 ± 0.08	0.84 ± 0.17	0.76 (0.25–2.14)	13	Dam 1979
	6	NP	NP	0.10 ± 0.56	0.17 ± 0.91	0.63		9	Lander1981
	11	NP	NP	4.8[b]	6[b]	0.8		9	Yerby 1990
	1	34.0	1	0.075	0.068	1.1		12	Iwasaki 2016
	22	NP	8	$33.49 \pm 13.04 \times 10^{-3}$	$77.44 \pm 27.39 \times 10^{-3}$	0.47 ± 0.21		10	Mygind 1976
	5	26.2 ± 3.3	3	$13.34 \pm 3.73 \times 10^{-3}$	$25.43 \pm 7.91 \times 10^{-3}$	0.57 ± 0.22		14	Kochenour 1980
	3	24.3 ± 1.5	0	$12.11 \pm 4.32 \times 10^{-3}$	$41.08 \pm 20.35 \times 10^{-3}$	0.39 ± 0.30		10	Lander 1977
	7	25.6 ± 4.3	4	$39.79 \pm 17.10 \times 10^{-3}$	$62.14 \pm 37.90 \times 10^{-3}$	0.75 ± 0.31		13	Dam 1979
	4	22.2 ± 4.1	1	$29.58 \pm 14.0 \times 10^{-3}$	$32.29 \pm 12.20 \times 10^{-3}$	0.98 ± 0.56		11	Landon 1979
	1	NP	1	26.05×10^{-3}	99.9×10^{-3}	0.26		8	Rapp 1979
Phenytoin	25	NP	NP	$16.67 \pm 21.74 \times 10^{-3}$	$41.67 \pm 111.11 \times 10^{-3}$	0.4	0.53 (0.13–2.29)	9	Lander 1981
	1	33.0	1	13.87×10^{-3}	19.02×10^{-3}	0.73		7	Perucca 1980
	14	NP	NP	1.04×10^{-3b}	0.6×10^{-3b}	1.74		9	Yerby 1990
	2	NP	NP	$57.45 \pm 19.76 \times 10^{-3}$	$26.49 \pm 6.72 \times 10^{-3}$	2.14 ± 0.20		9	Lander 1991
	8	23.6 ± 3.2	8	$26.48 \pm 11.06 \times 10^{-3}$	$35.97 \pm 25.81 \times 10^{-3}$	0.90 ± 0.41		14	Eadie 1992
	1	NP	NP	23.13×10^{-3}	57.77×10^{-3}	0.40		13	Perez-Lopez 1994
	36	NP	NP	11.63 ± 26.52	29.76 ± 61.35	0.39		14	Tomson 1994a
	2	37.0 ± 5.6	0	21.25 ± 16.07	39.24 ± 9.83	0.51 ± 0.28		13	Bernus 1995
	4	30.5 ± 3.1	2	27.27 ± 10.41	62.27 ± 31.53	0.49 ± 0.22		12	Iwasaki 2016
	1	24.0	0	0.01	0.02	0.55	0.62 (0.30–1.19)	5	Niebyl 1979
Primidone	1	NP	NP	0.01	0.03	0.43		9	Lander 1981
	2	29.5 ± 0.7	2	0.01 ± 0.002	0.02 ± 0.013	0.74 ± 0.63		13	Battino 1984
	1	23.0	0	0.01	0.03	0.39		14	Öhman 2002
Topiramate	10	NP (19.0–41.0)	NP	0.01 ± 0.03	0.03 ± 0.06	0.57	0.64 (0.40–0.91)	14	Öhman 2009
	11	28.0 (21.0–38.0)	NP	0.02 ± 0.007	0.03 ± 0.01	0.65 ± 0.13		15	Westin 2009
	3	NP	3	1.54 ± 10.0	1.69 ± 16.67	0.91		12	Reisinger 2013

(*continued on next page*)

Table 1 (*continued*)

Antiseizure medication	n	Age (years)	Monotherapy[a] (n)	3rd trimester	Baseline (pooled preconception & postpartum)	Alteration ratio	Combined alteration ratio	Quality	Reference
	3	24.3 ± 3.1	3	26.14 ± 11.35	46.34 ± 30.36	0.62 ± 0.53		12	Philbert 1985
	9	29.0 (22.0–37.0)	NP	50.0 ± 100.0	50.0 ± 50.0	1.0		11	Koerner 1989
	1	27.0	1	52.83	75.67	0.70	0.84 (0.12–1.22)	10	Kacirova 2010
Valproate	1	NP	1	5.0[b]	6.67[b]	0.75		12	Reisinger 2013
	2	28.5 ± 9.2	2	81.25 ± 30.05	94.5 ± 14.85	0.90 ± 0.46		12	Iwasaki 2016
	1	30.0	1	40.25[b]	113.17[b]	0.36		5	Rumpel 2017
	2	NP	NP	41.85 ± 11.34	58.86 ± 10.86	0.70 ± 0.06		15	Johannessen-Landmark 2018
	1	NP	1	3.85	8.33	0.46	0.57 (0.17–1.17)	12	Reisinger 2013
Zonisamide	1	28.0	0	0.04	0.06	0.63		12	Iwasaki 2016
	18	27.9 ± 4.7	14	0.028 ± 0.011	0.05 ± 0.016	0.58 ± 0.23		13	Reimers 2018

n: number of pregnancies, NA: not applicable, NP: not provided. The reason for differences between the reported size of the cohorts and the number of included patients in the ratio estimations are missing values at different time points. Dose-adjusted blood levels are provided in μg/mL per mg/day except for perampanel where values are ng/mL per mg/day. The quality column represents the quality scores assigned to the study using the ClinPK checklist. Provided values are means ± standard deviations.

[a] Or no co-medication with antiseizure medications with inducing properties.

[b] Estimated with daily doses per kg (mg/kg).

study investigated lamotrigine clearance patterns during pregnancy in 7 groups of patients with carriers of different genetic polymorphisms for UDP-glucuronosyltransferase (UGT) isoenzymes, which are involved in lamotrigine metabolism (Petrenaite et al., 2018). Alteration ratios ranged between 0.07 and 0.91 with a combined alteration ratio of 0.42. Combined alteration ratios were 0.98 (0.32–2.45, $n = 11$, k = 6) and 0.39 (0.07–2.13, $n = 261$, k = 16) in women with vs. without concomitant use of antiseizure medications with inducing properties. In the meta-analysis we reported a mean difference between 3rd trimester and baseline of -12.33×10^{-3} μg/mL per mg/day, 95%CI: -16.08 to -8.58×10^{-3}, $p < 0.001$; C/D levels were lower in the 3rd trimester (Fig. 1d). Observed heterogeneity was substantial ($I^2 = 100\%$, p < 0.001).

3.7. Levetiracetam

Data for levetiracetam derived from 12 studies ($n = 109$); alteration ratios ranged between 0.04 and 2.77 with a combined alteration ratio of 0.52. Combined alteration ratios were 0.90 (n = 1, k = 1) and 0.54 (0.04–2.78, $n = 50$, k = 6) in women with vs. without concomitant use of antiseizure medications with inducing properties. In the meta-analysis we reported a mean difference between 3rd trimester and baseline of −7.16 μg/mL per mg/day, 95%CI: −9.96 to −4.36, p < 0.001; C/D levels were lower in the 3rd trimester (Fig. 2a). Observed heterogeneity was substantial ($I^2 = 95\%$, $p < 0.01$).

3.8. Oxcarbazepine and monohydroxycarbazepine (MHD)

Evidence for oxcarbazepine (parent compound) derived from four cohorts ($n = 25$); alteration ratios ranged between 0.08 and 0.82 with a combined ratio of 0.42 (Table 1). No subgroup analysis stratifying for concomitant use of antiseizure medications with inducing properties was performed, as no data from women with concomitant antiseizure medications with inducing properties was available. The meta-analysis revealed a mean difference of -1.16×10^{-3} μg/mL per mg/day, 95% CI: -2.55 to 0.24×10^{-3}, $p = 0.10$ between 3rd trimester and baseline (Fig. 2b). Observed heterogeneity was substantial ($I^2 = 98\%$, $p < 0.01$). Four cohorts (n = 25) provided data for the main oxcarbazepine metabolite MHD; alteration ratios ranged between 0.06 and 1.44 with a combined ratio of 0.80 (Table 1). No subgroup analysis stratifying for concomitant use of antiseizure medications with inducing properties was performed, as no data from women with concomitant antiseizure medications with inducing properties was available. We estimated a mean difference of -4.87×10^{-3} μg/mL per mg/day, 95%CI: −9.39 to -0.35×10^{-3}, $p = 0.035$ between 3rd trimester and baseline (Fig. 2c). Observed heterogeneity was substantial ($I^2 = 85\%$, p < 0.01).

3.9. Perampanel

In one patient receiving a therapeutic regimen consisting of brivaracetam, lacosamide and perampanel, we estimated an alteration ratio of 1.63 for perampanel (Landmark et al., 2021).

3.10. Phenobarbital

Alteration ratios in six cohorts ($n = 39$) ranged between 0.37 and 1.80 with the combined ratio of 0.86 (Table 1). Combined alteration ratios were 0.75 (0.51–1.11, $n = 5$, k = 2) and 0.89 (0.68–1.10, $n = 4$, k = 2) in women with vs. without concomitant use of antiseizure medications with inducing properties. In the meta-analysis we estimated a mean difference of -47.19×10^{-3} μg/mL per mg/day, 95%CI: −120.96 to 26.58×10^{-3}, $p = 0.21$ between baseline and 3rd trimester with C/D levels being insignificantly lower in the 3rd trimester (Fig. 2d). Observed heterogeneity was substantial ($I^2 = 98\%$, p < 0.01).

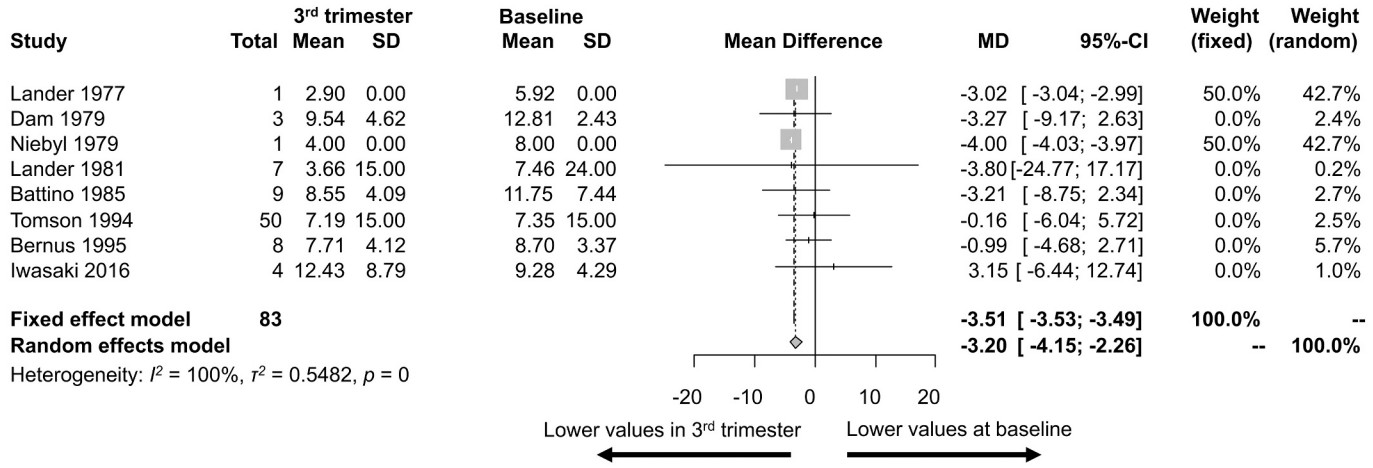
3.11. Phenytoin

Evidence for phenytoin derived from 15 cohorts ($n = 135$); alteration ratios ranged between 0.13 and 2.29 with a combined ratio of 0.83 (Table 1). Combined alteration ratios were 0.84 (0.13–3.06, n = 13, k = 5) and 0.78 (0.22–1.57, $n = 17$, k = 6) in women with vs. without concomitant use of antiseizure medications with inducing properties. In the meta-analysis we estimated a mean difference of -16.48×10^{-3} μg/mL per mg/day, 95%CI: −30.89 to -2.07×10^{-3}, $p = 0.025$ between 3rd trimester and baseline (Fig. 3a). Observed heterogeneity was substantial ($I^2 = 100\%$, $p < 0.001$).

3.12. Primidone

Alteration ratios for primidone (prescribed as such and not as active metabolite) in three cohorts (n = 4 patients) ranged between 0.30 and 1.19 with a combined ratio of 0.62. Combined alteration ratios were 0.55 (n = 1, k = 1) and 0.74 (0.30–1.19, $n = 2$, k = 1) in women with vs. without concomitant use of antiseizure medications with inducing properties. The meta-analysis revealed a mean difference of -13.78×10^{-3} μg/mL per mg/day, 95%CI: −22.69 to -4.87×10^{-3}, $p = 0.002$ (Fig. 3b). Observed heterogeneity was large ($I^2 = 100\%$, p < 0.001).

(a)



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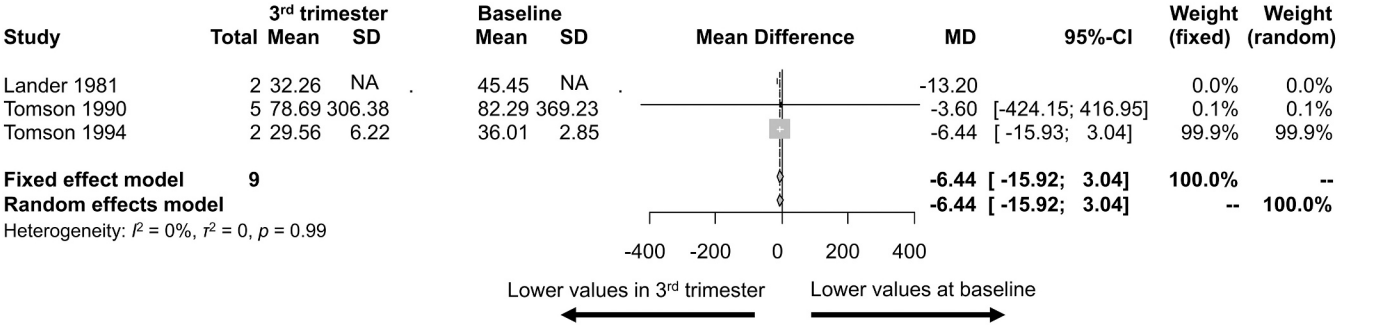

(c)

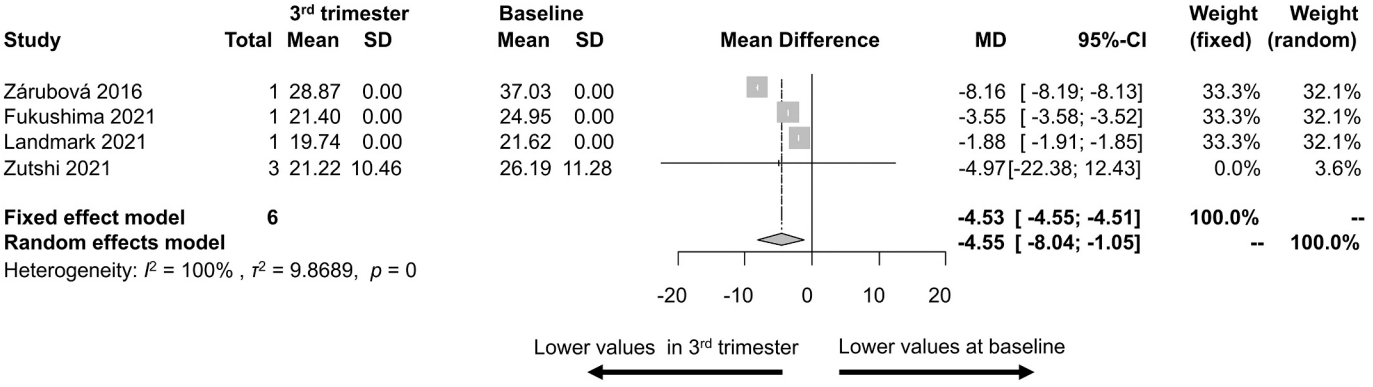

Fig. 1. a. Forest plot for differences in carbamazepine dose-adjusted concentrations between baseline and 3rd trimester (n = 83 from 8 studies). Values are provided in × 10^{-3} μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.
b. Forest plot for differences in ethosuximide dose-adjusted concentrations between baseline and 3rd trimester (n = 9 from 3 studies). Values are provided in μg/mL per mg/day. CI: confidence interval; MD: mean difference; NA: not available; SD: standard deviation.
c. Forest plot for differences in lacosamide dose-adjusted concentrations between baseline and 3rd trimester (n = 6 from 4 studies). Values are provided in × 10^{-3} μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.
d. Forest plot for differences in lamotrigine dose-adjusted concentrations between baseline and 3rd trimester (n = 188 from 21 studies). Values are provided in × 10^{-3} μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation; UGT: UDP-glucuronosyltransferase.

3.13. Topiramate

Evidence for topiramate derived from four cohorts (n = 25); alteration ratios ranged between 0.39 and 0.91 with a combined ratio of 0.64 (Table 1). Combined alteration ratios were 0.39 (n = 1, k = 1) and 0.91 (n = 3, k = 1) in women with vs. without concomitant use of

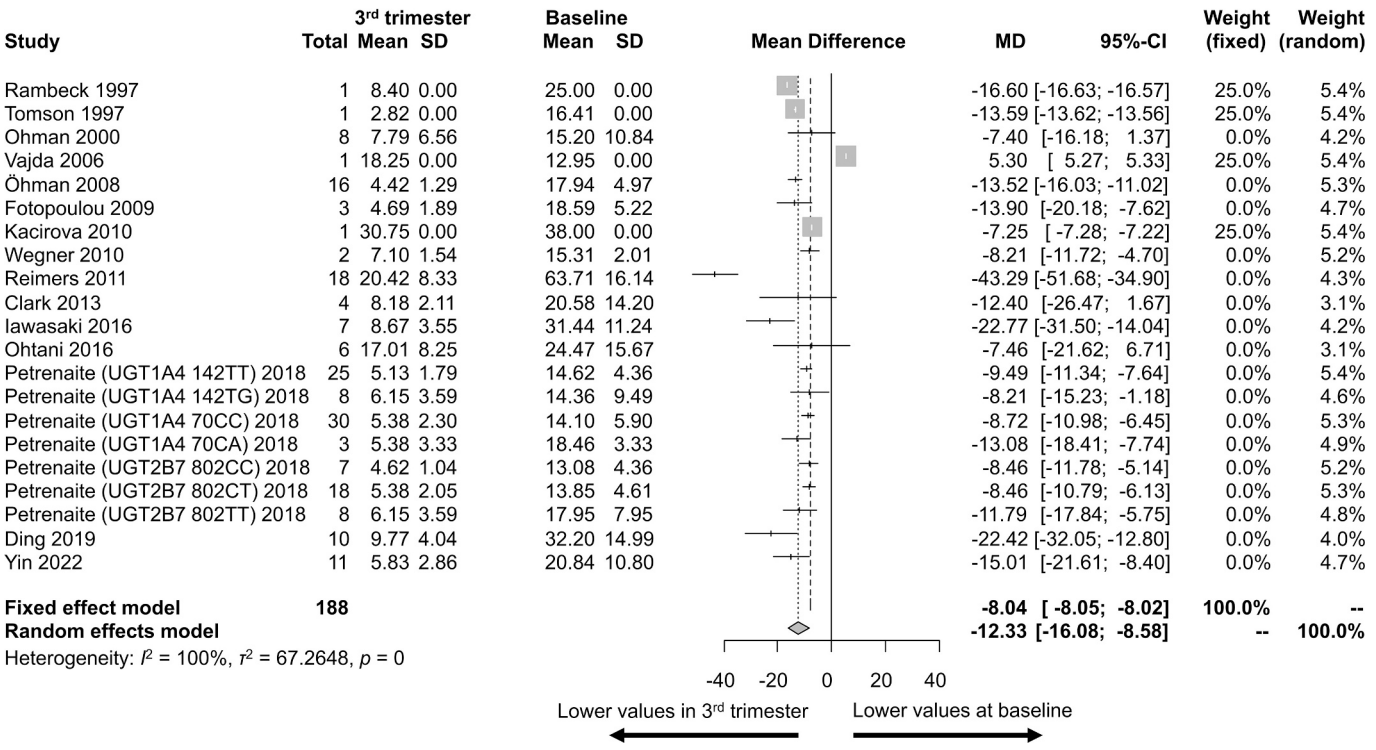

Fig. 1. (*continued*).

antiseizure medications with inducing properties. We estimated a mean difference of -15.12×10^{-3} μg/mL per mg/day, 95%CI: −25.45 to -4.79×10^{-3}, $p = 0.004$ between 3rd trimester and baseline (Fig. 3c). Observed heterogeneity was substantial ($I^2 = 82\%$, $p < 0.01$).

3.14. Valproate

Evidence for valproate derived from seven cohorts ($n = 19$); alteration ratios ranged between 0.12 and 0.1.22 with a combined ratio of 0.84 (Table 1). No subgroup analysis stratifying for concomitant use of antiseizure medications with inducing properties was performed, as no data from women with concomitant antiseizure medications with inducing properties was available.We estimated a mean difference of −22.83 μg/mL per mg/day, 95%CI: −22.86 to −22.81, p < 0.001 between 3rd trimester and baseline (Fig. 3d). Observed heterogeneity was minimal ($I^2 = 0\%$, $p = 0.91$).

3.15. Zonisamide

Evidence for zonisamide derived from three cohorts ($n = 20$); alteration ratios ranged between 0.33 and 0.96 with a combined ratio of 0.58 (Table 1). Combined alteration ratios were 0.50 (0.43–0.63, n = 3, k = 2) and 0.60 (0.33–0.96, $n = 17$, k = 2) in women with vs. without concomitant use of antiseizure medications with inducing properties.

3.16. Quality of included studies

The quality of the included studies was acceptable with an average rating score of 11.5 (Supplementary Table 2). Some variation is mainly explained by the lower quality in case reports, where authors provided less detail on the items outlined by the ClinPK checklist.

4. Discussion

Drug disposition is particularly important during pregnancy, since a decline in antiseizure medication levels may result in loss of seizure control with severe consequences for the mother as well as the fetus (Edey et al., 2014). Overtreatment, on the other hand, should be avoided given that teratogenic risks with some antiseizure medications are dose-dependent (Tomson et al., 2018). In our systematic review and meta-analysis, we assessed pregnancy effects on plasma concentrations of 15 commonly prescribed antiseizure medications by investigating alteration patterns between 3rd trimester and outside pregnancy. For several medications, such as for lamotrigine, levetiracetam, phenytoin, carbamazepine and valproate there is ample available data, whereas for others including brivaracetam and perampanel data derive from very small cohorts or even single patients. The observed fall for C/D levels could to some extent be explained by a decreased oral bioavailability of the drugs although enhanced elimination is likely to be more important (Pariente et al., 2016).

The lowest alteration ratios were reported for lamotrigine and oxcarbazepine being 0.42; this signifies that 3rd trimester plasma concentrations of lamotrigine and oxcarbazepine are on average 42% of baseline suggesting that lamotrigine and oxcarbazepine are largely affected by pregnancy-related changes in pharmacokinetics. These findings are in alignment with the estimates of the meta-analysis; for lamotrigine the mean difference of -12.33×10^{-3} μg/mL per mg/day between 3rd trimester and baseline indicates that with a lamotrigine dose of 400 mg/day, 3rd trimester concentrations would, on average, decrease by approximately 4.9 μg/mL. In light of the therapeutic reference range of lamotrigine of 1–6 μg/mL (Hiemke et al., 2018), this decrease represents a substantial change which is expected to lead to subtherapeutic lamotrigine levels (Reisinger et al., 2013). Thus, close clinical monitoring is required (Thangaratinam et al., 2018), with TDM enabling dose adjustments to mitigate pregnancy effects (Clark et al., 2013). The main mechanism mediating the pregnancy effects may

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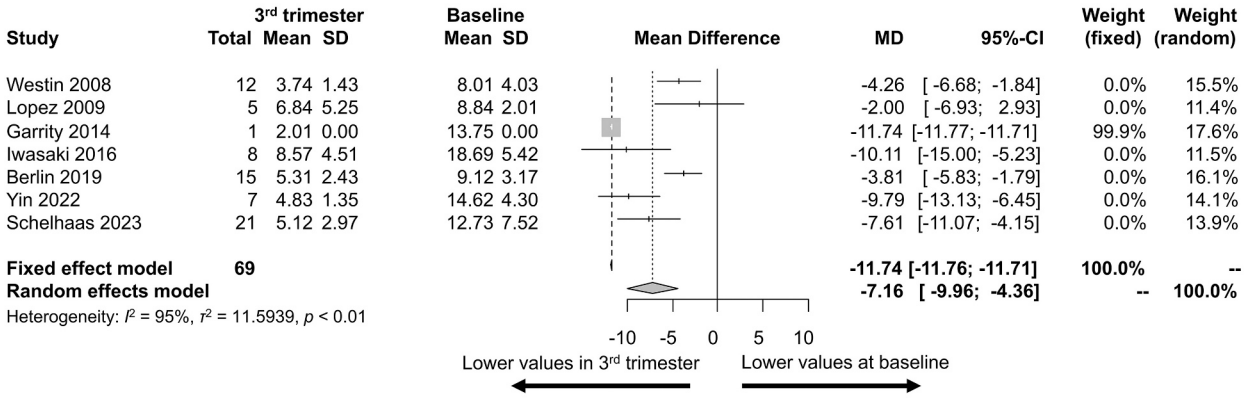

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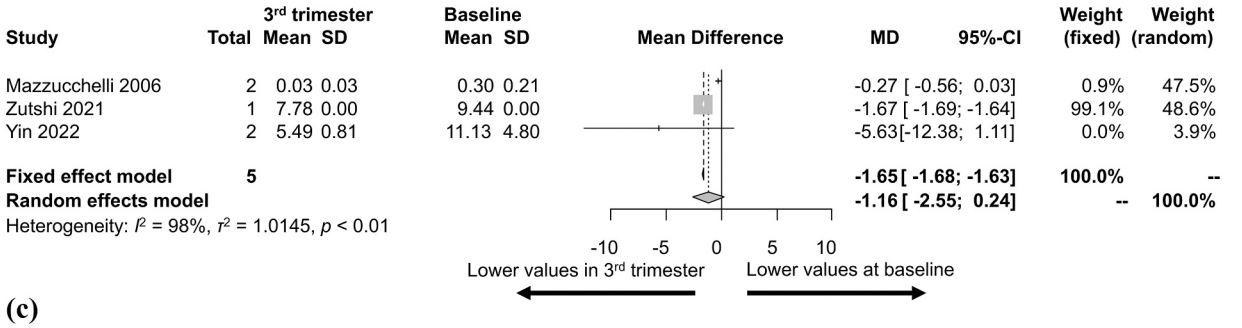

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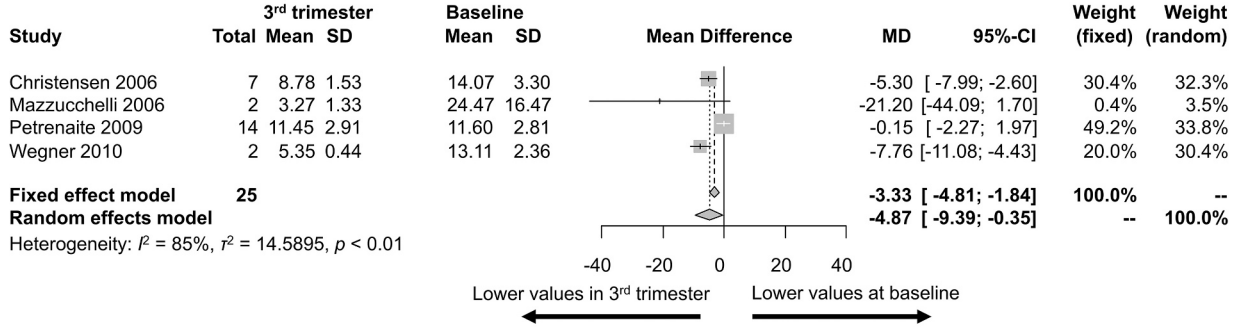

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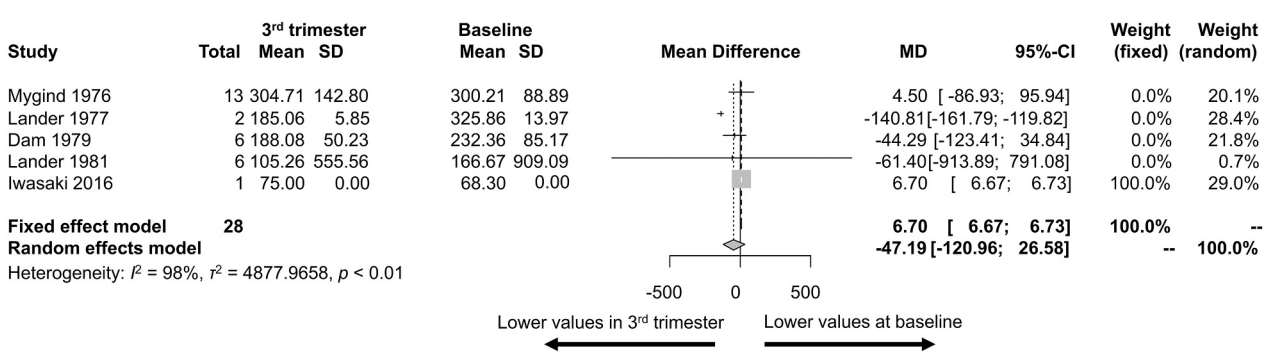

Fig. 2. a. Forest plot for differences in levetiracetam dose-adjusted concentrations between baseline and 3rd trimester (n = 69 from 7 studies). Values are provided in μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.
b. Forest plot for differences in oxcarbazepine dose-adjusted concentrations between baseline and 3rd trimester (n = 5 from 3 studies). Values are provided in $\times 10^{-3}$ μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.
c. Forest plot for differences in monohydroxycarbazepine (MHD) dose-adjusted concentrations between baseline and 3rd trimester (n = 25 from 4 studies). Values are provided in $\times 10^{-3}$ μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.
d. Forest plot for differences in phenobarbital dose-adjusted concentrations between baseline and 3rd trimester (n = 28 from 5 studies). Values are provided in $\times 10^{-3}$ μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.

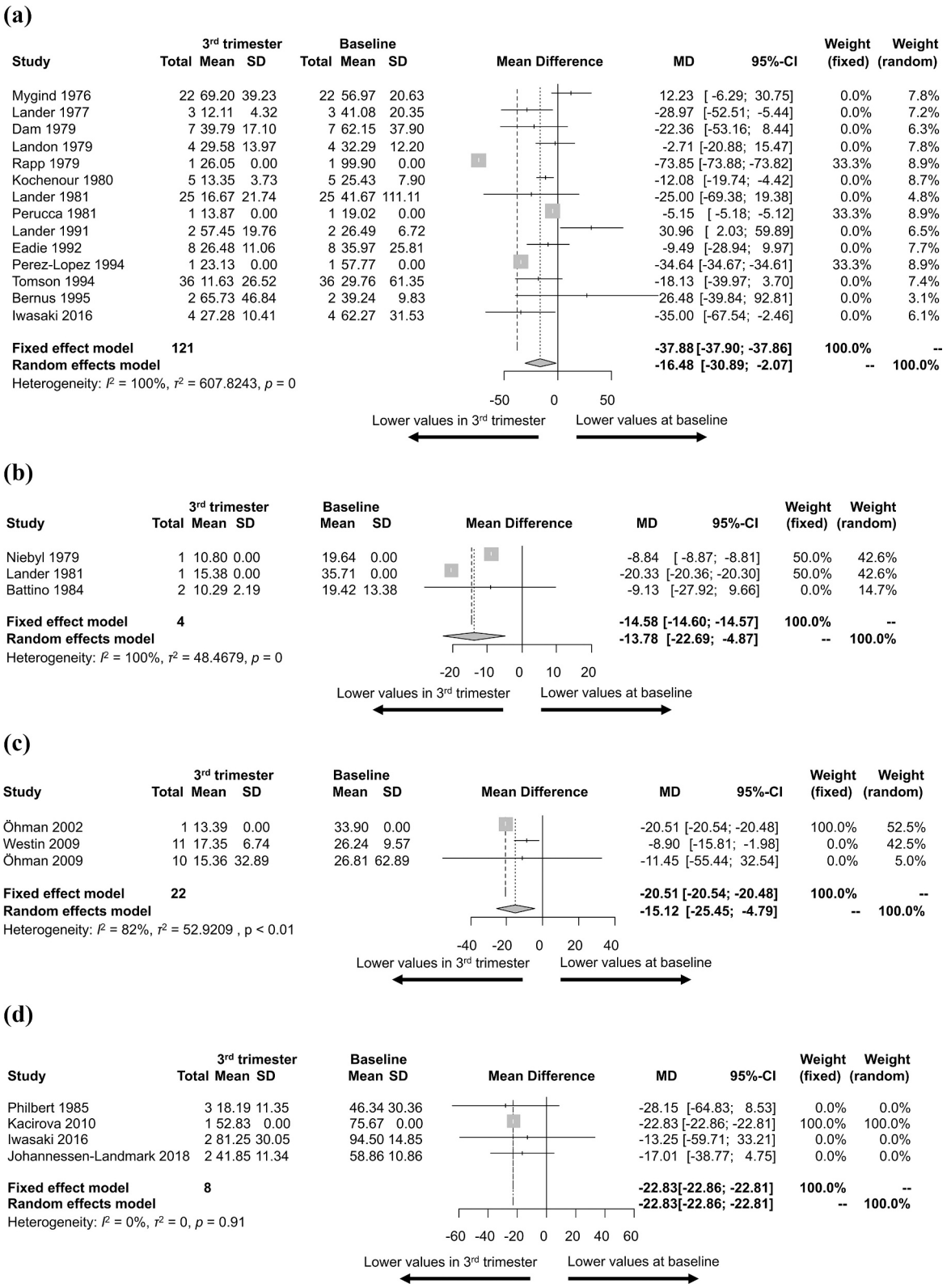

Fig. 3. a. Forest plot for differences in phenytoin dose-adjusted concentrations between baseline and 3rd trimester (n = 116 from 13 studies). Values are provided in $\times 10^{-3}$ μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.
b. Forest plot for differences in primidone dose-adjusted concentrations between baseline and 3rd trimester (n = 4 from 3 studies). Values are provided in $\times 10^{-3}$ μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.
c. Forest plot for differences in topiramate dose-adjusted concentrations between baseline and 3rd trimester (n = 22 from 3 studies). Values are provided in $\times 10^{-3}$ μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.
d. Forest plot for differences in valproate dose-adjusted concentrations between baseline and 3rd trimester (n = 8 from 4 studies). Values are provided in μg/mL per mg/day. CI: confidence interval; MD: mean difference; SD: standard deviation.

include the enzymes involved in the glucuronidation (Petrenaite et al., 2018) of lamotrigine, a principal metabolic pathway (Hiemke et al., 2018). Nevertheless, an investigation of changes in lamotrigine clearance during pregnancy in women with different uridine diphosphate glucuronosyltransferase (UGT) genetic polymorphisms found that the UGT variants did not influence the alternations in clearance during pregnancy (Petrenaite et al., 2018).

Like lamotrigine, evidence for oxcarbazepine suggested an increase in 3rd trimester clearance reflected by a combined alteration ratio of 0.42. However, when considering TDM data for oxcarbazepine, one needs to keep in mind that even at steady state the timing of the (presumable trough) blood sampling relative to time of drug intake might increase the scatter of C/D levels given the short elimination half-life of oxcarbazepine. The impact of pregnancy on the active metabolite of oxcarbazepine, MHD, was less pronounced, where we estimated a decrease of 20% (combined alteration ratio 0.80). However, the difference between 3rd trimester and baseline for C/D ratios was significant for MHD, but not for oxcarbazepine. We estimated mean differences of -1.16 and -4.87×10^{-3} μg/mL per mg/day for oxcarbazepine and MHD respectively, signifying that with an oxcarbazepine dose of 1800 mg/day, 3rd trimester concentrations would, on average, decrease by approximately 2.1 and 8.8 μg/mL respectively. Given that oxcarbazepine is a prodrug and considering a therapeutic reference range of the active metabolite MHD of 10–35 μg/mL (Hiemke et al., 2018), the pregnancy-related decrease of oxcarbazepine levels in the 3rd trimester may be critical. Accordingly, an investigation of thirteen pregnancies in ten women suggested that deterioration of seizure control during pregnancy was associated with the pregnancy-related decrease in MHD plasma concentrations compared to baseline concentrations (Petrenaite et al., 2009). Glucuronidation is also part of the metabolism of MHD and may account for the pregnancy effects on MHD clearance (Petrenaite et al., 2009). TDM may be valuable to orient oxcarbazepine dose adjustments, although authors have reported that dose increases during pregnancy may not always mitigate the decrease in the MHD plasma concentrations (Petrenaite et al., 2009).

Levetiracetam clearance may be also severely affected by pregnancy-related physiological changes affecting pharmacokinetics; we estimated a combined alteration ratio of 0.52 implying a two-fold increase of levetiracetam clearance in the 3rd trimester. As levetiracetam does not undergo extensive hepatic metabolism, we suspect that this increase in clearance is related to the increased glomerular filtration rate (GFR) observed in pregnancy (Westin et al., 2008). In the largest levetiracetam-treated cohort included in our meta-analysis, authors reported that low levetiracetam concentrations were associated with increased seizures in women that had had at least one seizure in the last year before pregnancy (Schelhaas et al., 2023). Therefore, it is recommended that TDM during pregnancy is utilized to detect pregnancy-related levetiracetam concentration changes in high-risk women with a goal to keep levetiracetam levels >65% of the baseline levels (Schelhaas et al., 2023).

Regarding other antiseizure medications, there were considerable data for carbamazepine, phenobarbital, phenytoin, topiramate and valproate as well as zonisamide. The pharmacokinetics of zonisamide was essentially affected by pregnancy as reflected by the alteration ratio of 0.57 (practically a decrease in the C/D ratio of 43% in the third trimester); the related mechanism may include an interplay between increased CYP3A4 activity, which is mainly involved in the metabolism of zonisamide and elevated renal excretion, whereas alterations regarding gastrointestinal absorption may also contribute (Reimers et al., 2018). The pharmacokinetics of phenytoin may be also affected by pregnancy with the alteration ratios suggesting a halving of C/D ratios in the 3rd trimester; nevertheless, given the non-linear kinetics of phenytoin, the use of C/D ratios may suffer from some limitations. In addition, decreased protein binding may contribute. We also reported a major change for C/D ratios in the mainly renally excreted topiramate (a decrease in C/D ratios of 36%), most likely due to the increased GFR (Westin et al., 2009), whereas for valproate and carbamazepine changes were less striking.

There was only one medication where we estimated reduced clearance in the 3rd trimester; for perampanel we estimated an alteration ratio of 1.63 suggesting decreased clearance in one single individual, which may not reflect the population mean. This finding is counterintuitive as the known metabolic pathways of perampanel, i.e. CYP3A4, CYP2B6 and UGT isoenzymes (Hiemke et al., 2018), display increased activity during pregnancy (Pariente et al., 2016). In other words, we may have expected an increased clearance of perampanel during pregnancy. However, our estimation of alteration ratio comes from one single woman whose 3rd trimester assessment of perampanel level was on the day of delivery (Landmark et al., 2021) a time of considerable physiologic changes. Data from larger cohorts in 3rd trimester are necessary to be able to make any conclusions regarding pregnancy effects on perampanel pharmacokinetics.

Of particular importance were the findings of the subgroup analysis stratifying for the impact of concomitant antiseizure medications with inducing properties; alteration ratios in women co-prescribed inducers were closer to 1.0 compared to women without, e.g. 0.98 vs. 0.39 respectively in case of lamotrigine. This implies that in women with concomitant antiseizure medication with inducing properties antiseizure medication levels during pregnancy may not highly deviate from levels in the non-pregnant state. One hypothesis underlying this finding could be the lack of further induction (or at least a much lower degree of induction) during pregnancy in women who already experienced induction due to concomitant antiseizure medication with inducing properties at preconception. The consequences of this finding are of major clinical relevance as dose adjustments to mitigate the impact of pregnancy may be less necessary in women with concomitant antiseizure medication with inducing properties.

4.1. Limitations

Compared to other medications, such as antipsychotic and antidepressant agents (Schoretsanitis et al., 2020; Westin et al., 2018b), the literature examining pregnancy-related pharmacokinetic changes for antiseizure medications is robust. Nevertheless, there are several limitations that need to be considered when interpreting the findings. First, nonadherence presents a major challenge for pharmacotherapy not least during pregnancy (de Korte et al., 2023), but was not considered in any of the included studies; thus, it cannot be excluded that changes regarding C/D levels might, at least partially, be attributed to nonadherence (Ruan et al., 2023). However, one would not expect nonadherence to vary with the type of antiseizure medications as to explain the differences we see between drugs in alterations in C/D levels. Second, only a small minority of studies assessed women on monotherapy, whereas many included women using concomitant pharmacotherapies during the time under study. Concomitant use of other drugs possessing inhibiting or inducing properties might have impacted plasma concentrations of the antiseizure medications included in our meta-analysis. In our subgroup analysis our focus was on the most likely interaction, induction of drug metabolism. We did not consider other, less likely interactions e.g. induction of glucuronidation by two interacting agents, but not enough induction to cope with the increased glucuronide load. Third, for several antiseizure medications, available evidence derives from single cases or small cohorts. Data with larger sample sizes was associated with greater heterogeneity, which implies a risk of Type II errors when assessing changes in the disposition of some medications. A consequence of the interindividual variability observed within larger cohorts is that one size does not fit it all, and only TDM combined with clinical assessment can enable treatment personalization. Fourth, some of the heterogeneity may be explained by differences of the analytical methods used. Fifth, post-dose intervals for trough samples strongly varied, with a number of studies lacking this detail. Sixth, the role of genetic variability is poorly understood. One single study investigated

clearance alteration patterns related genetic polymorphisms of enzymes involved in drug metabolism, by studying lamotrigine and UGT (Petrenaite et al., 2018). Evidence regarding the role of genetic polymorphisms of other enzymes, not at least within the CYP family, regarding other antiseizure medications were not available and the pharmacogenetic mechanisms in the context of pregnancy-related pharmacokinetic changes remain to be investigated. Seventh, another issue that has to be brought up is the fact that we assessed alterations in total concentrations, which may be misleading for highly protein bound drugs such as valproate, phenytoin and perampanel (Patsalos et al., 2017; Tomson et al., 1994). If a decline in total concentration is caused by a decrease in protein binding, the unbound pharmacologically active level may be unchanged, and this is also the concentration that reflects exposure to the fetus. Despite being more reliable when it comes to dosing, assessments of unbound concentration do not reflect mainstay of routine monitoring (and are frequently not available). However, it is important to be aware that total concentrations may underestimate drug exposure in situations with decreased binding to plasma proteins which occurs in pregnancy. Thus, we encourage futures studies to focus on assessments of unbound concentrations. Eight, the use of C/D levels implies linear kinetics, which may not hold for some medications, e.g. phenytoin due to saturation of the involved enzymes, with available data being less reliable. Ninth, compared to the 3rd trimester, concentrations in the 1st and 2nd trimester have received disproportionately less attention and future research will need to provide more data for these timepoints. Tenth, some antiseizure medications, such as lamotrigine or valproate, are also used in psychiatry; nevertheless, available TDM data (and data regarding the association of C/D ratios with clinical response) from pregnant women are, with one single exception (Clark et al., 2013), exclusively derived from cohorts with epileptic syndromes. Thus, no conclusions for the use of antiseizure medications in psychiatry can be drawn.

Despite these limitations the current literature allows for some practical recommendations for dose adjustments of antiseizure medications during pregnancy (Tomson et al., 2019; Agency MaHpR, 2021). Specifically, regular assessments of plasma concentrations for lamotrigine, levetiracetam and oxcarbazepine in women at high-risk for tonic-clonic seizures are strongly suggested to allow an individualized dose adjustment (Agency MaHpR, 2021), whereas in lack of blood levels, dose increases after the 1st trimester are expected to be required particularly in high-risk women (Tomson et al., 2019). In high-risk women we also recommend periodic TDM as integral part of management during pregnancy for the remainder of the studied antiseizure medications. Drug level monitoring during pregnancy is much more useful if an individual optimal drug level has been established before pregnancy. This can then serve as an individual reference level which is much more relevant than the general so called therapeutic reference intervals (Patsalos et al., 2008). Ultimately, the combination of intensive monitoring and good clinical assessments are expected to optimize pharmacological treatment of epilepsy during pregnancy.

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Authorship contributions

Participated in research design: GS, NK, CTS, KMD, SKS, OS, MP, PTH, MB, EK, DZ, EMP, TT.

Performed data analysis: NK, CTS, GS.

Wrote the manuscript: GS, OS, MP.

Edited and corrected the manuscript: GS, NK, CTS, KMD, SKS, OS, MP, PTH, MB, EK, DZ, EMP, TT.

CRediT authorship contribution statement

Georgios Schoretsanitis: Writing – original draft, Methodology, Investigation, Conceptualization. **Kristina M. Deligiannidis:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Nicholas Kasperk:** Writing – original draft, Methodology, Investigation, Conceptualization. **Chiara Theresa Schmidt:** Writing – original draft, Methodology, Investigation, Conceptualization. **Sarah Kittel-Schneider:** Writing – review & editing, Methodology, Investigation. **Peter Ter Horst:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Maya Berlin:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Elkana Kohn:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Eline M.P. Poels:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Deepti Zutshi:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Torbjörn Tomson:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Olav Spigset:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Michael Paulzen:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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Data availability

The code supporting the analyses of this study is available from the corresponding author upon reasonable request.

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Appendix A. Supplementary data

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