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ORIGINAL RESEARCH ARTICLE

Comprehensive Measurements of Intrauterine and Postnatal Exposure to Lamotrigine

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Abstract

Objective The aim of this study was to measure and investigate correlations of lamotrigine concentrations in maternal as well as umbilical cord blood, amniotic fluid, and breast milk to account for the distribution of the drug.

Methods Concentrations of lamotrigine were measured in 19 mother–infant pairs at the time of delivery. To account for the penetration ratio into amniotic fluid, cord blood and breast milk, the concentration of lamotrigine in the particular environment was divided by the concentration in maternal serum. A no-intercept model was applied for associations between maternal serum concentrations, amniotic fluid, umbilical cord blood, and breast milk concentrations.

Results The mean daily dosage of lamotrigine was 351.32 mg (range 50–650 mg). We detected associations between maternal serum and amniotic fluid ($\beta = 0.088$, $p < 0.001$), as well as umbilical cord ($\beta = 0.939$, $p < 0.001$) and breast milk ($\beta = 0.964$, $p < 0.001$). The median penetration ratio into amniotic fluid, cord blood, and breast milk was 0.68, 0.92, and 0.77, respectively.

Conclusions Lamotrigine concentrations in amniotic fluid, cord blood, and breast milk give evidence that the fetus/newborn is constantly exposed to lamotrigine. Maternal serum concentrations predicted exposure via amniotic fluid, umbilical cord, and breast milk. Data suggest that therapeutic drug monitoring can be recommended as part of the clinical routine in psychopharmacotherapy for pregnant or breastfeeding women.

Key Points

Fetal development in lamotrigine-medicated pregnant women takes place in an environment continuously exposed to lamotrigine.

Lamotrigine concentrations in maternal serum is a reliable predictor of its concentration in amniotic fluid, umbilical cord blood, and breast milk.

1 Introduction

Recommendations for the use of psychotropic drugs for the management of bipolar disorder or epilepsy during pregnancy remain inconsistent [1]. However, there is clear evidence for the need for great caution in the use of valproate in women of child-bearing age [2]. Clinical experience considering the safety of the majority of psychotropic drugs is lacking [3]. Hence, pharmacotherapy of perinatal psychiatric and neurologic diseases is complicated by the great concern for the safety of both mother and unborn child. The

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decision-making process is further complicated by the notion that the pregnancy outcome is influenced by the course of the untreated disease. Although untreated epilepsy does not seem to enhance the relative risk for congenital malformations considerably [4], the sequelae of untreated maternal psychiatric diseases cannot be ignored: there is evidence for the risk of future psychopathology [5], intrauterine growth retardation [6], preterm delivery [7], low birth weight [8], or even the for a risk of maternal suicidal behavior due to uncontrolled symptomatology [9].

Psychotropic and anticonvulsant drugs invariably cross the placental barrier, accessing the fetal circulation [10] depending on their physicochemical properties [11]. In particular, passive diffusion depends on properties related to the chemical drug structure as well as the compartmental pH, whereas pharmacokinetic parameters and physiological conditions such as protein binding, volume of distribution, renal plasma flow, and the glomerular filtration rate also play a vital role. The placenta disposes a multitude of transporters such as P-glycoprotein, multi-drug-resistance proteins, and others facilitating or preventing the passage of the drug. Through enzyme activity such as cytochrome P450 (CYP) or uridine diphosphate–glucuronosyltransferase (UGT), the placenta can metabolize a great diversity of pharmacologically active molecules eliciting or inhibiting fetotoxic effects [12].

Drug exposure after delivery continues in during breastfeeding and drug effects on infants are linked to the ability of a drug to penetrate into breast milk, getting access to the infants' circulation [13]. Parameters that influence the extent of the drug transport into breast milk include the half-life and oral bioavailability; protein plasma binding and drug lipophilicity may also be of crucial importance for drug penetration [14].

Lamotrigine, a second-generation anticonvulsant, possesses different chemical properties to other anticonvulsants. Its indication includes the adjunctive treatment of partial seizures in epilepsy and generalized seizures of Lennox–Gastaut syndrome. In psychiatric patients, lamotrigine is widely prescribed in bipolar disorder maintenance treatment when depressive symptoms are more prominent [15]. The main metabolic pathway of lamotrigine metabolism is a glucuronidation catalyzed by UGT1A4, leading to a major metabolite, lamotrigine-2-N-glucuronide. During pregnancy, high estrogen levels may increase lamotrigine clearance, since estradiol upregulates the expression of UGT1A4 [16]. Furthermore, low lamotrigine concentrations in pregnant patients might be explained in light of the placental expression of UGT1A isozymes accelerating the metabolism [17]. No appreciable increase in the rate of major congenital malformations was reported in 1558 first-trimester lamotrigine monotherapy exposures [18]; the malformation rate was 2.2%, which is close to the general population. A fetal exposure in 73 lamotrigine-medicated pregnant women was not associated with neurocognitive deficits in early childhood, as no child displayed an IQ under 70 [19]. Moreover, in a sample of 104 3- to 6-year-old children exposed to lamotrigine in utero, no adaptive behavior impairments were reported [20]. These data may explain the shift in prescription patterns of anticonvulsants in pregnant women, with lamotrigine being the most commonly prescribed drug [21].

The aim of the study was to analyze the distribution pattern of lamotrigine in maternal serum, amniotic fluid, umbilical cord blood and breast milk by measuring drug concentrations in the different environments. By assessing the relationship between the daily dose of lamotrigine, its concentrations in maternal serum, and drug concentrations in amniotic fluid, umbilical cord blood as well as breast milk, the study should help to predict the excess of in utero exposure as well as the exposure in breastfeeding conditions.

2 Materials and Methods

2.1 Patients

This investigation is part of an ongoing observational study examining the distribution pattern of various psychotropic agents in maternal blood, amniotic fluid, and umbilical cord blood at the time of delivery [22–25]. We further measure drug concentrations in breast milk to calculate the milk to plasma/serum ratio in breastfeeding mothers under psychopharmacological treatment. The study is being carried out as a collaboration between the Department of Psychiatry, Psychotherapy and Psychosomatics and the Department of Gynaecology and Obstetrics at the University Hospital of RWTH Aachen University, Aachen, Germany, beginning November 2012. The study protocol was approved by the local Ethics Committee. Part of the preliminary results have been previously published [25].

Data from 19 pregnant women, with age ranging from 19 to 39 years (mean age 30.4 ± 5.2 years; median 31 years), and 19 newborns are presented. Women received lamotrigine in daily doses between 50 and 650 mg throughout their pregnancy. The last dose adaptations took place 2 weeks before delivery. Three patients were co-medicated with levetiracetam (500, 1000, and 3000 mg/day) throughout the whole pregnancy, whereas two other patients were co-medicated with clobazam 25 mg/day (started some days before delivery). Except for one patient with a major depressive disorder (F33.4 according to the *International Classification of Diseases, 10th Revision* [ICD-10]) and an attention–deficit hyperactivity disorder (F90.0), all other patients were diagnosed with localization-related idiopathic epilepsy and epileptic syndromes with seizures of localized onset (G40.3).

2.2 Methods

The present study is a naturalistic prospective investigation of lamotrigine concentrations in maternal serum, amniotic fluid, and umbilical cord blood in 19 mother–infant dyads. Blood was taken at delivery under steady-state conditions with regard to the ingested drug but, due to clinical circumstances, not as trough concentrations. Amniotic fluid samples were available in 16 cases. In the case of nine breastfeeding women, maternal serum samples and milk samples were acquired at the same time in a timeframe of less than 30 min and not later than 3 days after delivery. Due to clinical circumstances, a trough concentration condition for the acquisition of serum and milk samples could not be guaranteed. No dose adjustments of lamotrigine were undertaken between the time of delivery and the acquisition of serum and milk samples.

Serum was prepared by centrifugation of blood samples at 14,171*g* for 15 min. Lamotrigine concentrations in maternal serum, amniotic fluid, umbilical cord blood, and breast milk were determined using the same analytic procedures with an isocratic high-performance liquid chromatography (HPLC) system with a UV detector using a reagent kit from Chromsystems Instruments & Chemicals GmbH (Graefelfing/Munich, Germany). The method is linear from the designated limit of quantification of 0.3 µg/mL up to the upper limit of 30 µg/mL for lamotrigine. Intra-assay precision and accuracy over a range from 2.7 to 10 µg/mL is $<2\%$ and inter-assay precision is $<6\%$. In one case the lamotrigine concentration in cord blood was below the limit of quantification of 0.3 µg/mL; in order to include this sample in the analysis we used the half of the limit of quantification (0.15 µg/mL), which is a common methodological strategy. Quantification details apply for all included types of human matrix (maternal serum, amniotic fluid, umbilical cord blood, and breast milk), but it should be noted that the method is only validated for human serum.

2.3 Statistical Analysis

To account for the penetration of lamotrigine into amniotic fluid, cord blood, and breast milk, we divided the drug concentrations of lamotrigine in amniotic fluid, cord blood, and breast milk by their counterpart concentrations in maternal serum, yielding a measure of the penetration ratio into amniotic fluid, cord blood, and breast milk (so-called milk:plasma/serum ratio [M:P]), respectively.

We performed a linear regression forced through the origin (no-intercept model) for associations between the parameters of interest, i.e., maternal serum, amniotic fluid, cord blood, and breast milk. Standardized coefficients β and standard errors (SEs) are reported. For all figures, intercept was suppressed. Statistical analyses were conducted with SPSS® (version 21; IBM, Armonk, NY, USA).

3 Results

Obstetrical outcome data, data on daily doses, and serum, amniotic fluid, cord blood, and breast milk concentrations of lamotrigine are shown in Table 1. Obstetrical outcome data are available for all infants. Two deliveries were preterm (i.e., <37 weeks gestational age). Eight infants were temporarily admitted to the intensive care unit; one infant was prenatally diagnosed with DiGeorge syndrome with an interrupted aortic arc type B and a ventricle septal defect, whereas another infant showed signs of a respiratory distress syndrome and one infant showed a slow feeding syndrome. A ventricle septal defect was diagnosed in one child that concomitantly suffered from intestinal malrotation. A third case of cardiac defect included a persistent foramen ovale in an infant with a co-morbid laryngomalacia. Furthermore, there was another newborn with signs of respiratory distress syndrome; for this particular infant, congenital genitourinary anomalies including double kidneys and ureteral dilatation were diagnosed. Another newborn displayed increased C-reactive protein (CRP) and interleukin (IL)-6 levels (12.5 mg/L and 61.96 pg/mL, respectively), whereas one newborn had signs of a neonatal adaptation syndrome. Except for one infant with low birth weight (i.e., <2.5 kg), all other newborns were within a range between the 5th and the 85th percentiles. The average lamotrigine daily dose was 351.32 mg (standard deviation [SD] 154.6, range 50–650 mg). Lamotrigine concentrations in maternal serum were in a range between 0.3 and 8.4 µg/mL, (mean 3.63 µg/mL, SD 2.09 µg/mL, therapeutic reference range 1–6 µg/mL [26]). Amniotic fluid concentrations ranged between 0.5 and 8.3 µg/mL (mean 2.8 µg/mL, SD 1.9 µg/mL), whereas cord blood concentrations were between 1.1 and 6.2 µg/mL (mean 2.98 µg/mL, SD 1.44 µg/mL); in one case, cord blood concentrations were below the limit of quantification (0.3 µg/mL). Lamotrigine concentrations in the breast milk of nine mothers were between 1.57 and 6.1 µg/mL (mean 2.73 µg/mL, SD 1.64 µg/mL).

We detected associations between maternal serum and amniotic fluid ($\beta = 0.088$, $p < 0.001$, SE = 0.094) as well as umbilical cord ($\beta = 0.939$, $p < 0.001$, SE = 0.63) and breast milk ($\beta = 0.964$, $p < 0.001$, SE = 0.058; see Fig. 1).

The penetration ratio into amniotic fluid ranged between 0.31 and 1.69 (SD 0.43, mean 0.82, median 0.68, quartile [Q] 1: 0.58, Q3: 0.91); the penetration ratio into the fetal circulation, calculated on basis of umbilical cord blood concentrations, was between 0.19 and 2.25 (SD 0.43, mean 0.88, median 0.92, Q1: 0.58, Q3: 1.00). The M:P ratio was in a

Table 1 Patients' characteristics and clinical characteristics of 19 mothers taking lamotrigine during pregnancy and their infants

Patient	Maternal age (years)	Gestational age at delivery (weeks)	Mode of delivery	Body weight (g)	Weight percentile	Infant sex	APGAR	DD lamotrigine (mg)	Lamotrigine MS (µg/mL)	AF (µg/mL)	Ratio AF/MS	CB (µg/mL)	Ratio CB/MS	Lamotrigine MSII (µg/mL)	BM (µg/mL)	Ratio BM/MSII	Co-medication	Outcome/birth defect
1	35	38 + 6	Section	2900	10th	♂	9/10/10	650	6.53	3.8	0.58	6.2	0.95	n.p.	n.p.	n.p.	Clobazam 25 mg	Monitoring
2	26	35 + 6	Spontaneous	3170	83rd	♀	9/9/9	600	3.3	2.47	0.75	2.65	0.8	n.p.	n.p.	n.p.	Levetiracetam 3000 mg	Preterm, monitoring
3	31	34 + 1	Section	2440	37th	♂	7/9/9	200	1.1	0.75	0.68	1.4	1.27	1.1	1.57	1.43		Preterm, respiratory distress syndrome, hyperbilirubinemia
4	27	38 + 1	Section	3270	44th	♂	9/10/10	500	2.9	0.9	0.31	1.4	0.482	n.p.	n.p.	n.p.		PROM, DiGeorge syndrome, interrupted aortic arc type B, VSD
5	19	37 + 5	Section	2600	7th	♂	10/10/10	400	6.2	2.8	0.45	4.8	0.77	n.p.	n.p.	n.p.	Clobazam 25 mg	Slow feeding of newborn
6	34	38 + 4	Section	3395	62th	♀	9/10/10	350	4.1	2.8	0.68	2.4	0.59	3.0	2.2	0.73		
7	27	39 + 3	Spontaneous	2930	13th	♀	8/9/10	300	1.2	0.9	0.75	2.7	2.25	2.4	1.6	0.67		
8	36	41 + 2	Spontaneous	3500	29th	♂	9/10/10	500	3.8	2.5	0.66	3.8	1	8.7	6.1	0.7	Levetiracetam 500 mg	
9	29	40 + 1	Spontaneous	3380	40th	♀	9/10/10	200	0.3	0.5	1.67	<0.3	n.c.	n.p.	n.p.	n.p.		
10	28	39 + 6	Spontaneous	3050	17th	♀	9/10/10	225	2.6	n.p.	n.p.	2.6	1	n.p.	n.p.	n.p.	Levetiracetam 1000 mg	VSD, intestinal malrotation
11	35	39 + 6	Section	3040	16th	♀	9/10/10	350	3.4	n.p.	n.p.	3.6	1.06	8.9	5	0.56		
12	21	38 + 4	Section	3540	74th	♀	9/10/10	250	3.4	3.2	0.94	1.9	0.56	3.4	1.9	0.59		PFO, laryngomalacia
13	38	38 + 6	Section	3225	29th	♂	9/10/10	250	1.9	1.3	0.68	2.1	1.11	n.p.	n.p.	n.p.		
14	26	38 + 0	Spontaneous	3055	39th	♀	9/10/10	600	4.9	8.3	1.69	3.1	0.63	n.p.	n.p.	n.p.		

Table 1 (continued)

Patient	Maternal age (years)	Gestational age at delivery (weeks)	Mode of delivery	Body weight (g)	Weight percentile	Infant sex	APGAR	DD lamotrigine (mg)	Lamotrigine MS (µg/mL)	AF (µg/mL)	Ratio AF/MS	CB (µg/mL)	Ratio CB/MS	Lamotrigine MSII (µg/mL)	BM (µg/mL)	Ratio BM/MSII	Co-medication	Outcome/birth defect
15	25	41 + 1	Spontaneous	4210	85th	♂	8/8/8	200	5.8	4.7	0.81	1.1	0.19	n.p.	n.p.	n.p.		Respiratory distress syndrome, right double kidney, ureteral dilatation
16	31	40 + 3	Spontaneous	3690	66th	♀	10/10/10	500	1.8	n.p.	n.p.	1.8	1	1.8	2.3	1.28		CRP 12.5 mg/L, IL-6 61.96 pg/mL
17	39	39 + 3	Spontaneous	3725	78th	♀	9/10/10	300	8.4	3.2	0.38	5.1	0.61	5.9	1.9	0.32		
18	20	40 + 6	Spontaneous	2870	5th	♀	9/10/10	50	2.5	3.8	1.52	2.3	0.92	2.8	2	0.71		
19	27	39 + 0	Section	3170	23rd	♂	9/10/10	250	4.9	2.9	0.59	4.7	0.96	n.p.	n.p.	n.p.		Neonatal adaptation syndrome

AF amniotic fluid, *BM* breast milk, *CB* cord blood, *CRP* C-reactive protein, *DD* daily dosage, *IL-6* interleukin-6, *MS* maternal serum with at the time of delivery, *MSII* maternal serum at the time of milk sampling, *n.c.* not possible to calculate, *n.p.* not provided, *PFO* persistent foramen ovale, *PROM* premature rupture of membranes, *VSD* ventricular septal defect, ♀ female, ♂ males

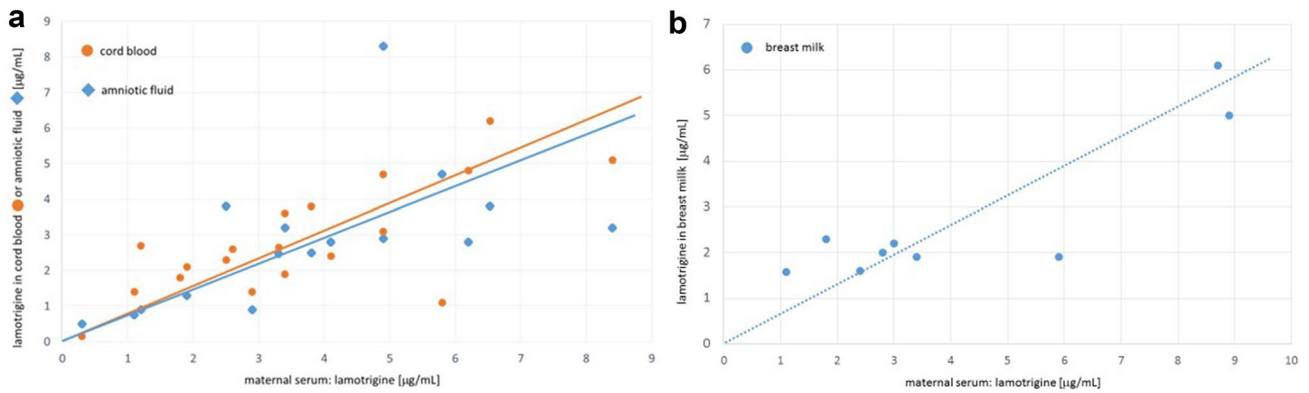

Fig. 1 Associations were detected between maternal serum and amniotic fluid ($\beta = 0.088$, $p < 0.001$, SE = 0.094) as well as umbilical cord ($\beta = 0.939$, $p < 0.001$, SE = 0.63) (**a**) and breast milk ($\beta = 0.964$, $p < 0.001$, SE = 0.058) (**b**), indicating that maternal serum concentrations allow to quantify fetal in utero exposure and drug exposure in case of breastfeeding constellations with lamotrigine. *SE* standard error

range between 0.32 and 1.43 (mean 0.77, SD 0.35, median 0.77, Q1: 0.56, Q3: 1.00) (see Fig. 2).

4 Discussion

Across anticonvulsants, lamotrigine is one of the most commonly prescribed drugs for neurologic and psychiatric indications [21]. Therefore, data capturing the distribution patterns in maternal and umbilical cord blood, amniotic fluid, and breast milk are necessary in order to assess fetal/newborn exposure.

Our findings allow some valuable conclusions. First, they provide a comprehensive overview of fetal/newborn exposure to lamotrigine via different routes of exposure (intrauterine and breastfeeding exposure) and our data demonstrate that the development occurs in an environment of pharmacologically relevant concentrations of lamotrigine. Second, the findings show a strong correlation between maternal serum drug concentrations and amniotic fluid as well as cord blood and breast milk concentrations of lamotrigine. These correlations had already been reported in the preliminary analysis supporting the importance of therapeutic drug monitoring (TDM) during pregnancy to assess drug exposure of unborn and breastfed children exposed to lamotrigine [25]. A significant correlation between maternal serum and umbilical cord blood drug concentrations has also been demonstrated by other researchers [27].

With regard to the ability of lamotrigine to enter fetal circulation, the penetration ratio into umbilical cord blood was calculated with a median of 0.92, which was slightly lower than the median ratio reported in a cohort of nine women (1.01) [28], but very close to the median ratio provided in a bigger sample (0.91, $n = 45$) [27]. Data providing lamotrigine concentrations in amniotic fluid other than our own preliminary results are lacking [25]. Apparently, the values of drug concentrations in the preliminary cohort did not manage to capture the variability of the penetration ratio into amniotic fluid. Findings in our bigger cohort (19 vs. 6 patients) suggest a higher median penetration ratio (0.68 vs. 0.58) into amniotic fluid. The M:P ratio of 0.77 calculated here was considerably higher than the ratio reported in a

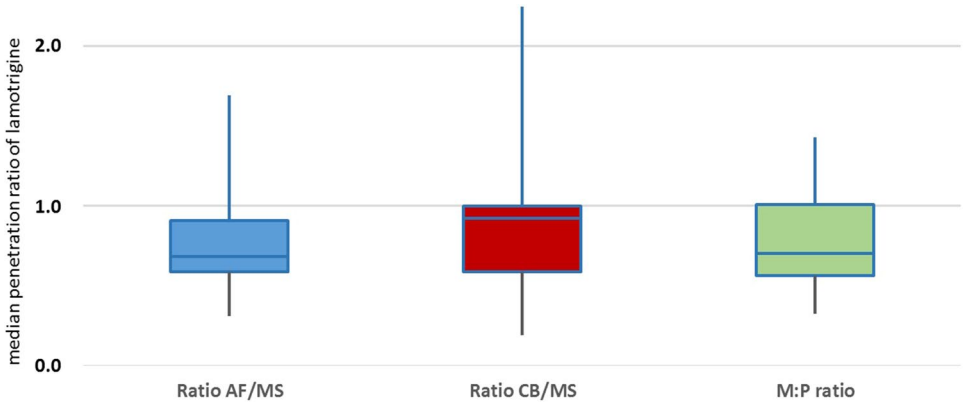

Fig. 2 Boxplot of the penetration ratios into amniotic fluid (left; median 0.68, Q1: 0.58, Q3: 0.91; range 0.31–1.69), into the fetal circulation (middle; median 0.92, Q1: 0.58, Q3: 1.00; range 0.19–2.25) and into breast milk (right; median 0.77, Q1: 0.56, Q3: 1.00, range 0.32–1.43). *AF* amniotic fluid, *CB* cord blood, *MS* maternal serum, *M:P* milk:plasma/serum ratio, *Q* quartile

previous study where researchers collected multiple breast milk samples, computing a minimum, mean, and maximum penetration ratio of 0.27, 0.41, and 0.63, respectively [29]. Likewise, a prospective study of four breast milk samples reported a median ratio of 0.59 [28]. Our M:P ratio was almost twofold higher than the M:P ratio of Newport et al. [29] and considerably higher than the ratio provided by Fotopoulou et al. [28], perhaps due to the fact that the collection of breast milk took place in the first days of milk production and most likely consisted of colostrum. However, one has to consider a high variability of breast milk concentrations of lamotrigine, which has been previously reported by Newport et al. [29], and recommendations regarding breastfeeding under lamotrigine treatment may be discussed in light of a potential drug accumulation in the infant due to inefficient glucuronidation [30]. Lamotrigine is metabolized mainly by UGT1A4, with a minor contribution by UGT2B7 and UGT1A3 [31]. During intrauterine development, very low UGT enzyme activity has been described in hepatic samples. However, after birth, UGT activity is continuously increasing during the first months; nevertheless, at the age of 2 years UGT activities are estimated up to 40-fold lower than those of adults have been described [32]. Thus, prescribers need to consider the potential of lamotrigine accumulation in breastfed infants due to the lack of UGT activity during the first months. Therefore, even if lamotrigine-medicated mothers are recommended to breastfeed [33], monitoring of adverse drug reactions is highly indicated [34]. In addition, genetic polymorphisms in UGT1A4 and UGT2B7 leading to lower glucuronidation activity have been described and might affect individual lamotrigine glucuronidation. Thus, the almost equally high drug exposure of the infant during prenatal development and after birth compared with the concentrations in maternal plasma may carry the risk of adverse lamotrigine effects due to the individual low metabolizing capacity in the infant. Knowing the child's genetic profile of drug-metabolizing enzymes and transporters (such as UGT1A4 or UGT2B7) may be considered as a future tool for maternal dose adjustment during pregnancy or breastfeeding in order to reduce drug exposure and adverse effects in the infant.

Our data may contribute to a critical debate regarding the indicated daily dosage of lamotrigine for pregnant women: hepatic and renal function changes during pregnancy may lead to lamotrigine metabolism alterations carrying significant clinical consequences such as an enhanced frequency of seizures or relapse in bipolar disorder [35]. Thus, clinicians need to consider maternal drug concentrations of lamotrigine as a more precise predictor of fetal exposure than daily dosage. On the other hand, register data report a dose-dependent risk of malformations for pregnant patients receiving lamotrigine as monotherapy with a cut-off daily dosage of 300 mg [36]. The data presented here underscore the need to apply the lowest doses and stable serum concentrations to maintain treatment efficacy in order to avoid an overload of the placental barrier in the course of very high serum concentrations [9]. Our findings underscore the role of maternal serum concentrations as good indicators for fetal/newborn exposure. Consequently, TDM can be a valuable tool to understand the different routes of drug access to the fetus or newborn and thereby ensure patient-matched psychopharmacotherapy even during pregnancy [26]. The available data suggest that treatment of epilepsy or even mood disorders such as bipolar disorder during pregnancy with lamotrigine seems to be relatively safe in terms of major congenital malformations [37]. While a recent retrospective study of six mothers receiving lamotrigine for their entire pregnancy reported a relatively high prevalence of low birth weight (33%) [38], we found only one newborn with a birth weight less than 2.5 kg (5.5 lb), taking into account that half of the aforementioned sample was under co-medication with other psychotropic drugs such as quetiapine and nortriptyline. Cardiac defects have been previously reported, particularly in mothers receiving daily dosages of lamotrigine ≥ 300 mg [36]. In our cohort, cardiac defects occurred in three cases in two mothers with low daily doses (200 and 225 mg/day) and in one case of an applied daily dose of 500 mg, with serum concentrations between 2.6 and 3.4 µg/mL. This leads to a frequency of 17% for cardiac malformations in our sample, which is much higher than the risk reported in the literature but must be seen in the context of the small sample size [39]. Considering this discrepancy requires a debate about the reproductive safety of lamotrigine and requires larger study sample sizes in future studies. A craniofacial defect was observed in one of the newborns, but existing evidence does not suggest an enhanced relative risk [40]. Another newborn displayed a congenital renal disorder; there are reports of renal defects in the literature for newborns exposed to lamotrigine, but the risk is considered to be similar to that of the general population [36].

Our study presents some shortcomings. Data from larger cohorts will further advance knowledge in the field. A specific limitation of our work is the lack of information regarding dose adjustments for our patients throughout their pregnancy. Therefore, we were not able to address the hypothesis that dose adjustments may be necessary during pregnancy given the increased lamotrigine elimination. As no multiple measurements per patient were available, we were also unable to apply population pharmacokinetic modelling and simulation strategies [41], which could have uncovered the effects of additional relevant parameters such as the actual time of last dose intake and of blood sampling. These data were not acquired and, therefore, we were not able to consider them in our analysis.

5 Conclusion

Despite the limitations of the study due to its observational nature, the data outline the role of TDM in quantifying fetal exposure and development under lamotrigine exposure. Maternal serum concentrations essentially reflect drug concentrations in amniotic fluid and fetal circulation and can be used to predict lamotrigine exposure in the unborn child or breastfed infant.

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Compliance with Ethical Standards

Author contributions Drs. Saßmannshausen, Franz, Schoretsanitis, Stingl, Augustin, Gründer, and Paulzen participated in the research design of the study. Drs. Schoretsanitis and Paulzen performed the initial statistical analyses. Dr. Schoretsanitis and Dr. Paulzen wrote the first article draft. All authors contributed to the interpretation of data and approved the final manuscript.

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Conflict of interest Gerhard Gründer has served as a consultant for Allergan (Dublin, Ireland), Boehringer Ingelheim (Ingelheim, Germany), Eli Lilly (Indianapolis, IN, USA), Janssen-Cilag (Neuss, Germany), Lundbeck (Copenhagen, Denmark), Ono Pharmaceuticals (Osaka, Japan), Otsuka (Chiyoda, Japan), Recordati (Milan, Italy), Roche (Basel, Switzerland), Servier (Paris, France), and Takeda (Osaka, Japan). He has served on the speakers' bureau of Eli Lilly, Janssen Cilag, Neuraxpharm (Langenfeld, Germany), Lundbeck, Otsuka, Recordati, Roche, Servier, and Trommsdorf (Aachen, Germany). He has received grant support from Boehringer Ingelheim and Roche. He is co-founder of Mind and Brain Institute GmbH (Zornheim, Germany) and Brainfoods GmbH (Zornheim, Germany). He reports no conflict of interest with this publication. Michael Paulzen, Julia C. Stingl, Marc Augustin, Helena Saßmannshausen, Cordula Franz, and Georgios Schoretsanitis had no conflicts of interest during the last 12 months.

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