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Toward Precision Dosing of Lamotrigine During Pregnancy: Physiologically Based Pharmacokinetic Modeling and Simulation

Yudie Qian[1,2,3] | Wanhong Wu[1,2] | Chengjie Ke[1,2] | Siting Liu[1,2,3] | Jiarui Chen[1,2,3] | Yuying Chen[1,2,3] | Xianzhong Guo[1,2] | Weiwei Lin[1,2]

[1]Department of Pharmacy, The First Affiliated Hospital, Fujian Medical University, Fuzhou, People's Republic of China | [2]Department of Pharmacy, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou, People's Republic of China | [3]The School of Pharmacy, Fujian Medical University, Fuzhou, People's Republic of China

Correspondence: Xianzhong Guo (9477101@qq.com) | Weiwei Lin (lww13705063157@163.com)

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ABSTRACT

Lamotrigine is a commonly used anti-seizure medication in pregnant women. However, its pharmacokinetics (PK) during pregnancy markedly change, increasing the frequency of seizures and endangering the safety of the mother and fetus. Meanwhile, insufficient PK data on lamotrigine during pregnancy hinders its dose adjustment. This study aimed to predict the maternal and fetal PK of lamotrigine and provide recommendations for dose adjustment. A physiologically based pharmacokinetic (PBPK) model of lamotrigine was constructed using PK-Sim and MoBi and validated with clinical data. The area under the steady-state concentration–time curve (AUC) for lamotrigine decreased by 66.5%, 71.1%, and 81.2% during early, mid, and late pregnancy, respectively, compared with non-pregnant conditions. To achieve effective exposure, three, three, and five times the baseline dose were recommended during early, mid, and late pregnancy, respectively. The fetal PK was best predicted using the isolated cotyledon perfusion method compared to the Caco-2 cell permeability and MoBi default methods. Based on the fetal risk concentration (4.87 mg/L), during early, mid, and late pregnancy, the maximum recommended once-daily dosage should not exceed 400, 500, and 700 mg, respectively, and the twice-daily dosage should not exceed 300, 400, and 600 mg, respectively. The significant decrease in lamotrigine exposure may increase the frequency of seizures in pregnant women. Therefore, prompt dose adjustment is recommended to control seizures while ensuring fetal safety.

1 | Introduction

Epilepsy is a common chronic disorder of the brain, with an estimated prevalence of 0.3%–0.5% in pregnant women [1]. Moreover, 14%–32% of pregnant women with epilepsy experience a higher frequency of seizures [2]. Pregnant women with epilepsy face a heightened risk of mortality, and their children are twice as likely to have congenital abnormalities compared to those born to mothers without epilepsy [3].

Epilepsy requires anti-seizure medications (ASMs) to control seizures, especially during pregnancy. However, ASM selection in pregnancy has changed considerably, with a gradual decline in the use of valproic acid and carbamazepine and a corresponding

Yudie Qian and Wanhong Wu are co-first authors. Xianzhong Guo and Weiwei Lin are both corresponding authors.

Summary

- What is the current knowledge on the topic?
  - Lamotrigine is widely used in treating epilepsy. Marked changes in its pharmacokinetics during pregnancy may increase seizure frequency, threatening the safety of the mother and fetus and requiring dose adjustments. However, dose adjustments of lamotrigine during pregnancy remain unclear.
- What question did this study address?
  - This study illustrates how to adjust lamotrigine doses in pregnant women with epilepsy during pregnancy to control maternal seizures while keeping the fetus safe.
- What does this study add to our knowledge?
  - The area under the concentration–time curve of lamotrigine is substantially reduced during pregnancy. Three, three, and five times the baseline dose is recommended for early, mid, and late pregnancy, respectively. However, considering fetal safety, the maximum recommended once-daily dose should not exceed 400, 500, and 700 mg, and the twice-daily dose should not exceed 300, 400, and 600 mg in early, mid, and late pregnancy, respectively.
- How might this change drug discovery, development, and/or therapeutics?
  - Understanding the maternal–fetal pharmacokinetics of lamotrigine in pregnancy and providing dosage recommendations can facilitate more precise lamotrigine dosing in pregnant women to manage seizures and ensure fetal safety.

increase in lamotrigine use [4]. Lamotrigine (Lamictal) is a second-generation ASM widely used in the pregnant population due to its low incidence of congenital malformations [5]. Lamotrigine is 90% metabolized via the glucuronidation pathway, with the remaining 10% excreted in the urine as a prototype [6]. The metabolic enzymes involved in the lamotrigine glucuronidation pathway are UDP-glucuronosyltransferase (UGT)1A4, UGT1A3, and UGT2B7 [7]. However, UGT2B7 seems to have no considerable effect on lamotrigine glucoside formation. Moreover, UGT1A4 metabolizes drugs 10-fold higher than UGT1A3 [8].

Seizure frequency during pregnancy may increase owing to reduced plasma lamotrigine concentrations associated with altered pharmacokinetics (PKs) [9]. On average, plasma lamotrigine concentrations decrease by 68% during pregnancy [10]. Additionally, clearance (CL) increases by up to 300% during pregnancy compared to non-pregnancy [11]. The corresponding low plasma concentrations lead to poor efficacy and seizures, jeopardizing the lives of the mother and fetus [12]. Therefore, dosage adjustment is recommended for lamotrigine during pregnancy.

Large amounts of lamotrigine can penetrate the placenta, with potential negative outcomes [13]. For example, a 16-day-old infant reportedly suffocated after receiving an overdose of lamotrigine administered by the mother, and the level of lamotrigine in the fetus' blood at the time of asphyxiation was measured to be 4.87 mg/L [14]. This suggests that the dose must be limited during pregnancy to ensure fetal safety. Therefore, PK studies of lamotrigine in fetuses are important for toxicity guidance and dosing adjustment.

To our knowledge, no studies have reported on maternal–fetal PK properties, and the U.S. Food and Drug Administration has not made recommendations on the lamotrigine dosage for pregnant individuals. Furthermore, the limited studies on fetal exposure to drugs and the challenges in obtaining cord plasma samples have hindered the prediction of pharmacokinetic profiles of fetuses. Meanwhile, physiologically based pharmacokinetic (PBPK) modeling can simulate the concentration–time drug profiles within physiologically realistic structures of the human body, including drug PK in pregnant women and fetuses, which are difficult to assess in clinical trials [15].

This study aims to predict the maternal and fetal PK of lamotrigine using a maternal–fetal PBPK model and provide recommendations for dose adjustments during pregnancy to control seizures in pregnancy while ensuring fetal safety, filling a gap in the clinical understanding of lamotrigine during pregnancy.

2 | Methods

2.1 | Software

The lamotrigine PBPK model for non-pregnant women was developed using PK-Sim. The nine unique compartments of pregnant women were added using MoBi and exported to PK-Sim for population modeling. The observed plasma concentration–time data were digitized using GetData Graph Digitiser 2.22. Statistical data were analyzed, and illustrations were produced using Excel and OriginPro 2022 software, respectively.

2.2 | General Workflow

First, a healthy non-pregnant model was developed and validated in PK-Sim. Second, the model was updated through MoBi, and the parameter values were adjusted according to the changes observed during pregnancy. The completed pregnancy model was then imported into PK-Sim to simulate populations at different gestation periods and validated using data from published literature. Third, placental permeability parameters derived from three methods were applied to the model, and the predictions were compared using clinical data to select the most appropriate method to describe fetal PK. Finally, based on the PBPK models, the PK for early, mid, and late pregnancy was predicted, and dosage recommendations for pregnant women were provided. The workflow is illustrated in Figure 1.

2.3 | Development of a PBPK Model for Non-Pregnant Women

The PBPK model for the non-pregnant population was constructed using PK-Sim classical construction. It comprises the brain, heart, lungs, liver, kidneys, adipose tissue, muscle, and

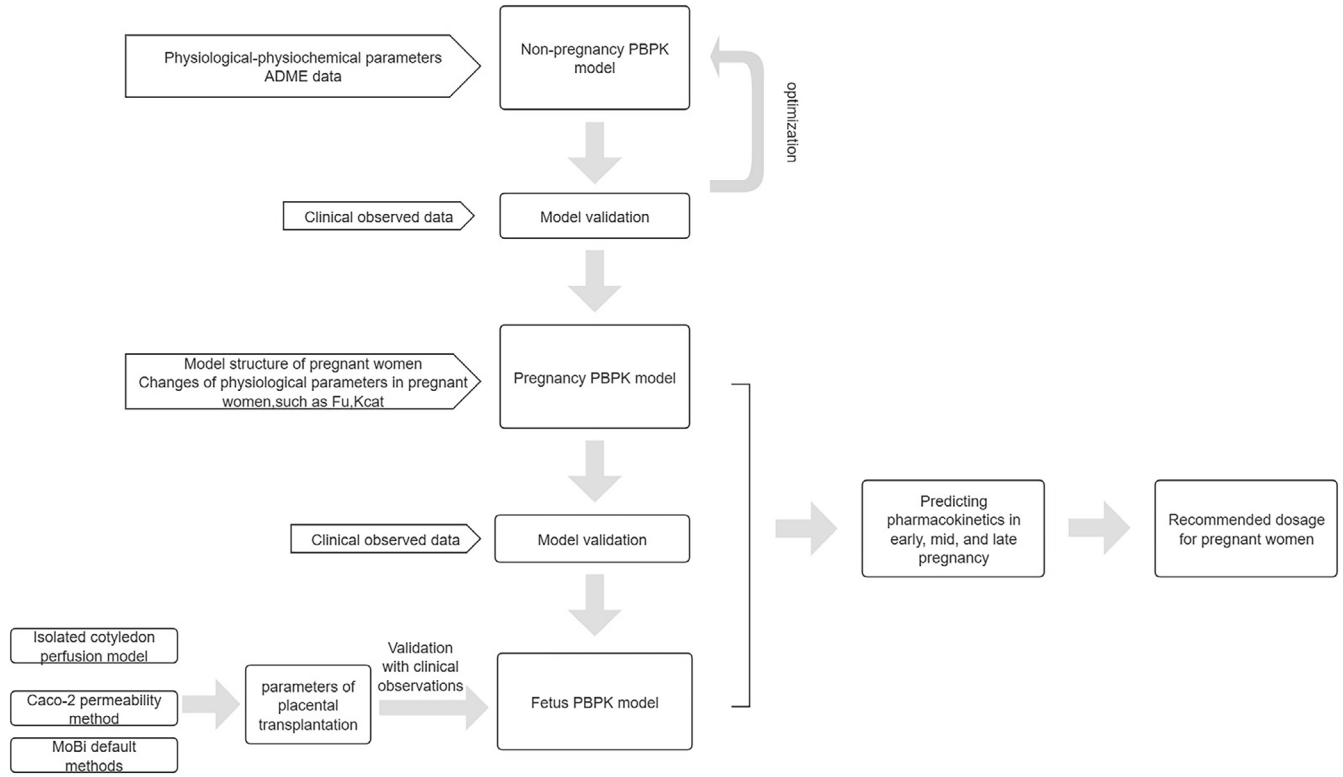

FIGURE 1 | Workflow for the development and evaluation of the PBPK model for pregnancy. ADME, absorption, distribution, metabolism, excretion; Fu, drug fraction unbound; Kcat, catalytic rate constant; PBPK, physiology-based pharmacokinetics.

skin. Parameters, such as lipophilicity, fraction of unbound drug in plasma (Fu), acid dissociation constant (pKa), and solubility of lamotrigine, were obtained from DrugBank and published articles (Table S1) [8, 16–20]. The maximum rates of the enzyme-catalyzed reaction (V_{max}) of 153 and 812 pmol/min/mg were obtained from different literature and initially applied to construct the PBPK model, respectively [8, 19]. The V_{max} of 812 pmol/min/mg better fit the observations (Figure S1) and was then selected to be incorporated into the model.

2.4 | Development of a PBPK Model for Pregnant Women

The non-pregnancy PBPK models built with PK-Sim were sent to MoBi with nine specific pregnancy compartments added to the classic PK-Sim structure: breasts, amniotic fluid, myometrium, endometrium, fetus, placenta fetal, placenta maternal, and the arterial and venous blood pools of the umbilical cord [21]. The model was imported into PK-Sim to construct PBPK models for early (1–13 weeks), mid (14–28 weeks), and late (29–42 weeks) pregnancy. The reference group included non-pregnant women (20–40 years old), with 100 individuals per population.

The Fu and catalytic rate constant (Kcat) were altered for different pregnancy periods. The non-pregnancy Kcat of UGT1A4 calculated by the software was 7.52 1/min. First, the ratios of plasma lamotrigine-2-N-glucuronide (2-N-GLUC) produced by UGT1A4 concentrations to plasma lamotrigine concentrations at different periods were extracted from the plot generated by Ohman et al. [22] (Figure S2). Next, the enzyme activities (Kcat) of UGT1A4 were calculated (Table S2) during early, mid, and late pregnancy using Equation (1):

$$\text{Enzymatic activity at different gestations} = \frac{P_{2\text{-N-GLUC/lamotrigine}}}{N_{2\text{-N-GLUC/lamotrigine}}} \times 7.52 \quad (1)$$

where P represents the 2-N-GLUC/lamotrigine plasma concentration ratio at different gestational periods and N represents the 2-N-GLUC/lamotrigine plasma concentration ratio during the non-pregnancy period. No information was available regarding variations in UGT1A3 activity during pregnancy; therefore, UGT1A3 activity was not altered. The Kcat and Fu values during pregnancy are presented in Table S2.

The Fu and serum albumin concentrations of lamotrigine at different gestational periods were calculated from the non-pregnant population using Equations (2) and (3), as follows: [23]

$$\text{Fu} = \frac{1}{1 + KA \times P} \quad (2)$$

$$P = 14.7\exp(-0.045x) + 31.7 \quad (3)$$

where Fu is the fraction of unbound drug in plasma, P is the drug concentration bound to protein, KA is the equilibrium association constant, and x is the number of weeks since fertilization. KA was calculated for non-pregnancy from Equation (2), after which the mean albumin values were estimated based on

Equation (3) and, by extension, provided Fu values for pregnancy. In addition, the standard deviation (SD) of albumin (5.33) was also included [23] and used to calculate the SD of Fu.

2.5 | PK Prediction of Lamotrigine During Pregnancy

According to the manufacturer's instructions, the common daily dose range of lamotrigine is 100–700 mg. Therefore, once-daily dosage regimens of 100–700 mg and twice-daily dosages of 50–350 mg were simulated to compare the differences in the PK of lamotrigine between non-pregnancy and pregnancy. The changes in PK during pregnancy were compared with the results of previous studies [24–27] to assess the PK prediction accuracy. Dosage recommendations were made for different pregnancy periods.

2.6 | Assessment of Placental Permeability

Isolated cotyledon perfusion, Caco-2 cell permeability, and the MoBi default methods were used to evaluate the passive fusion clearance through the placenta (D_{pl}) and the partition coefficient between the fetus and the mother ($K_{f,m}$), which were incorporated into the fetal model. Fetal clinical data [13, 28–31] were then added to select the most appropriate method for describing the fetal PK by comparing the magnitude of the fold error in the predicted and clinically observed fetal concentrations. The dose regimens and demographics are summarized in Table S3.

The basal four-chamber model of the isolated cotyledon was constructed in MoBi based on a previous study [32]. Subsequently, based on the experimental lamotrigine perfusion data in isolated cotyledons [33], the initial concentration of the maternal storage chamber was modified to 1.9 μmoL, and the flow rates of the maternal and fetal reservoirs were set to 9 mL/min and 5 mL/min, respectively. The partition coefficient was optimized to 0.81 by fitting the observed data. The differential equations (Equations (4–7)) associated with the isolated cotyledon perfusion model have been described in a previous study: [32]

Maternal reservoir:

$$\frac{dc_m}{dt} = \frac{Q_m}{V_m} \times \left(\frac{C_{mp}}{kp_{pl}}\right) - C_m \tag{4}$$

Maternal cotyledon:

$$\frac{dc_{mp}}{dt} = \frac{\left(Q_m \times \left(C_m - \frac{C_{mp}}{kp_{pl}}\right) - D_{cot} \times \left(C_{mp} - C_{fp}\right)\right)}{V_{mp}} \tag{5}$$

Fetal cotyledon:

$$\frac{dc_{fp}}{dt} = \frac{\left(Q_f \times \left(C_f - \frac{C_{fp}}{kp_{pl}}\right) + D_{cot} \times \left(C_{mp} - C_{fp}\right) - k_{pe} \times C_{fp} \times V_{fp}\right)}{V_{fp}} \tag{6}$$

Fetal reservoir:

$$\frac{dc_f}{dt} = \frac{Q_f}{V_f} \times \left(\frac{C_{fp}}{kp_{pl}} - C_f\right) \tag{7}$$

where C_m is the maternal concentration (mg/L), Q_m is the flow rate of the maternal compartment (L/h), V_m is the maternal compartment volume (L), C_{mp} is the maternal cotyledon concentration (mg/L), Kp_{pl} is the placental partition coefficient, D_{cot} is the passive diffusion clearance (L/h), C_{fp} is the fetal cotyledon concentration (mg/L), V_{mp} is the maternal placenta volume (L), Q_f is the flow rate of the fetal compartment (L/h), C_f is the fetal concentration (mg/L), K_{pe} is the placental elimination (h^{-1}), V_{fp} is the foetal placenta volume (L), and V_f is the fetal compartment volume (L).

D_{cot} was obtained after fine-tuning the lamotrigine PBPK-isolated cotyledon perfusion model, while D_{pl} was estimated using Equation (8):

$$D_{pl} = \frac{D_{cot} \times V_{pl}}{V_{cot}} \tag{8}$$

where D_{pl} (mL/min) is the transplacental passive diffusion clearance, D_{cot} (mL/min) is the cotyledon diffusion parameter, and V_{pl} (mL) and V_{cot} (mL) are the volumes of the placenta and the cotyledons, respectively.

In the Caco-2 cell permeability method, the $P_{app,x}$ value was modified to the mean apparent permeability of lamotrigine through a Caco-2 cell monolayer (7.37×10^{-5} cm/s) according to Equation (9) to calculate the transplacental passive diffusive clearance of lamotrigine in vivo [34]. This formula has been specifically described in a previous study, as shown below: [35]

$$CL_{pD,u,X} = \frac{\overline{P_{app,X}}}{\overline{P_{app,\text{midazolam}}}} \times CL_{pD,u,\text{midazolam}}(L/h) \tag{9}$$

where $CL_{PD,u,X}$ is the in vivo transplacental passive diffusion clearance of lamotrigine, $\overline{P_{app,X}}$ is the average apparent membrane permeability of lamotrigine, $\overline{P_{app,\text{midazolam}}}$ is the average apparent membrane permeability of midazolam (489.9 nm/s), and $CL_{PD,u,\text{midazolam}}$ is the optimized in vivo transplacental passive diffusion clearance of midazolam (500 L/h).

The default calculation method in open system pharmacology software is to derive the corresponding intestinal permeability based on the physicochemical properties of a drug (i.e., lamotrigine's effective molecular weight and membrane affinity) [36]. The method assumes that the placental and intestinal permeability are the same. Herein, the fixed calculated permeability was multiplied by the surface area of the chorionic villi (11.8 m^2) at a specific age of fertilization to obtain D_{pl} [37].

2.7 | Model Validation

The accuracy of the PBPK model in non-pregnant women was confirmed using PK data from clinical observations of lamotrigine. The dose regimens and demographic data are presented

in Table S4 [38–43]. Therapeutic drug monitoring (TDM) data for patients with epilepsy taking oral lamotrigine at the First Affiliated Hospital of Fujian Medical University, China, in 2022–2023 were collected to develop a goodness-of-fit (GOF) plot for further validation, and the predictions were compared to the observations. This study was approved by the institutional review board of the First Affiliated Hospital of Fujian Medical University (China). The model achieved accurate predictions when the fold error was 0.5–2, particularly close to 1. The fold error was calculated using Equation (10):

$$\text{Fold error} = \frac{\text{Predicted}}{\text{Observed}} \tag{10}$$

For validation, clinical observational data of lamotrigine in pregnant women were collected and viewed as trough concentrations. The dose regimens and demographics are summarized in Table S5 [13, 30, 31, 44–46].

3 | Results

3.1 | Validation of the PBPK Model in Non-Pregnant Women

The PBPK model simulations of lamotrigine for a healthy non-pregnant population are shown in Figure 2a–f. The predicted and observed values were generally consistent, and the fold errors of the maximum plasma drug concentration (C_{max}) and the area under the plasma concentration–time curve (AUC) were all within 0.5–2 (Table S6). To further validate the PBPK model, a GOF plot of steady-state trough concentrations of TDM data was collected from the hospital for 25 female patients with epilepsy treated with lamotrigine; the predicted deviations were within two-fold (Figure 2g). Hence, the PBPK model was successfully created. It can accurately characterize the PK of lamotrigine in a non-pregnant population and is capable of expansion in pregnant populations.

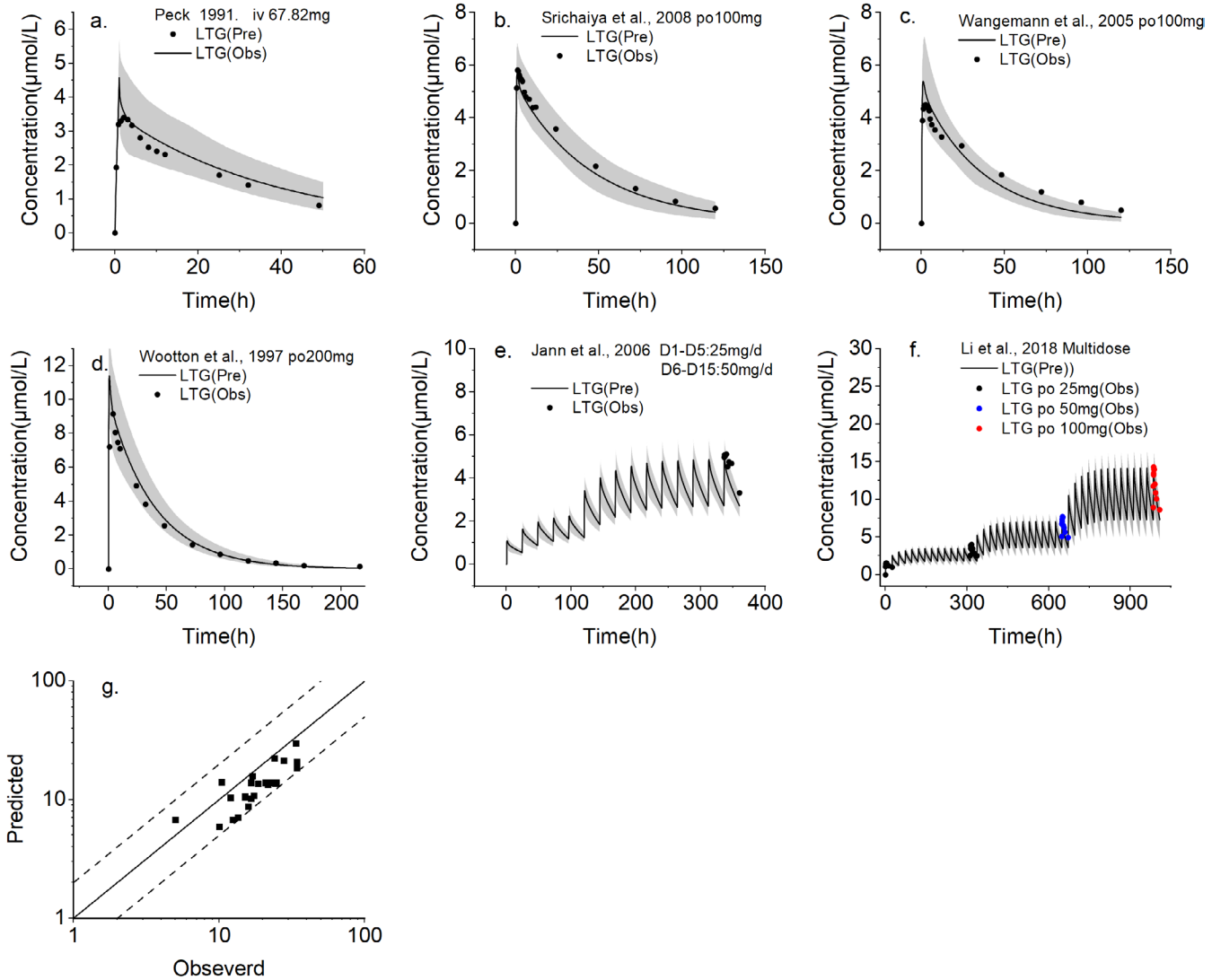

FIGURE 2 | Predicted mean plasma concentration–time profiles after lamotrigine administration for non-pregnant women. (a) Intravenous 67.82 mg; (b, c) oral 100 mg; (d) oral 200 mg; (e) oral 25 mg/d from D1 to D5, 50 mg/d from D6 to D15; (f) oral 25 mg/d from D1 to D14; 50 mg/d from D15 to D28; 100 mg/d from D29 to D42. (g) Lamotrigine non-pregnant population goodness-of-fit plot. Dotted line, two-fold error range; black line, mean predicted curve; shaded areas, 5%–95% predicted range; closed dots, clinical observations of lamotrigine; D, day.

3.2 | Validation of the PBPK Model in Pregnant Women

The PBPK simulation results for dose-normalized concentrations (concentration/dose (μmol/L/mg)) of lamotrigine in pregnant women at different stages of pregnancy are shown in Figure 3a–c. Most of the observed data of lamotrigine were within 5%–95% of the simulated predictions. The GOF plot further confirmed that all predicted values were within a two-fold error of the observed values (Figure 3d).

Compared to the pre-pregnancy baseline, the predicted AUC in early, mid, and late pregnancy decreased by an average of 66.5%, 71.1%, and 81.2%, respectively. The CL in early, mid, and late pregnancy increased by an average of 72.9%, 81.9%, and 128.3%, respectively. The maximum steady-state plasma drug concentrations during a dosage interval ($C_{max,ss}$) in early, mid, and late pregnancy decreased by an average of 45.7%, 50.9%, and 59.6%, respectively. The minimum steady-state plasma drug concentration during a dosage interval ($C_{min,ss}$) in early, mid, and late pregnancy decreased by an average of 58.8%, 64.1%, and 75.7%, respectively (Table 1). The predicted decreases of $C_{min,ss}$ were compared with those observed in clinical longitudinal studies (Figure S3), with fold errors close to 1. This suggested that the model effectively predicted trough concentrations of lamotrigine during pregnancy.

3.3 | Comparison of Three Different Methods of Placental Permeability

The isolated cotyledon perfusion, Caco-2 cell permeability, and MoBi default methods were used to assess the placental permeability of lamotrigine. In the isolated cotyledon perfusion model, the predicted maternal and fetal umbilical vein concentrations were similar to the observed values (Figure 4), demonstrating the model's ability to accurately derive placental permeability parameters. The specific permeability parameters derived from the three methods are shown in Table S7.

The fetal umbilical vein PK curves and fold errors of the predicted and observed fetal umbilical vein blood concentrations using these methods are shown in Figure 5 and Table S8,

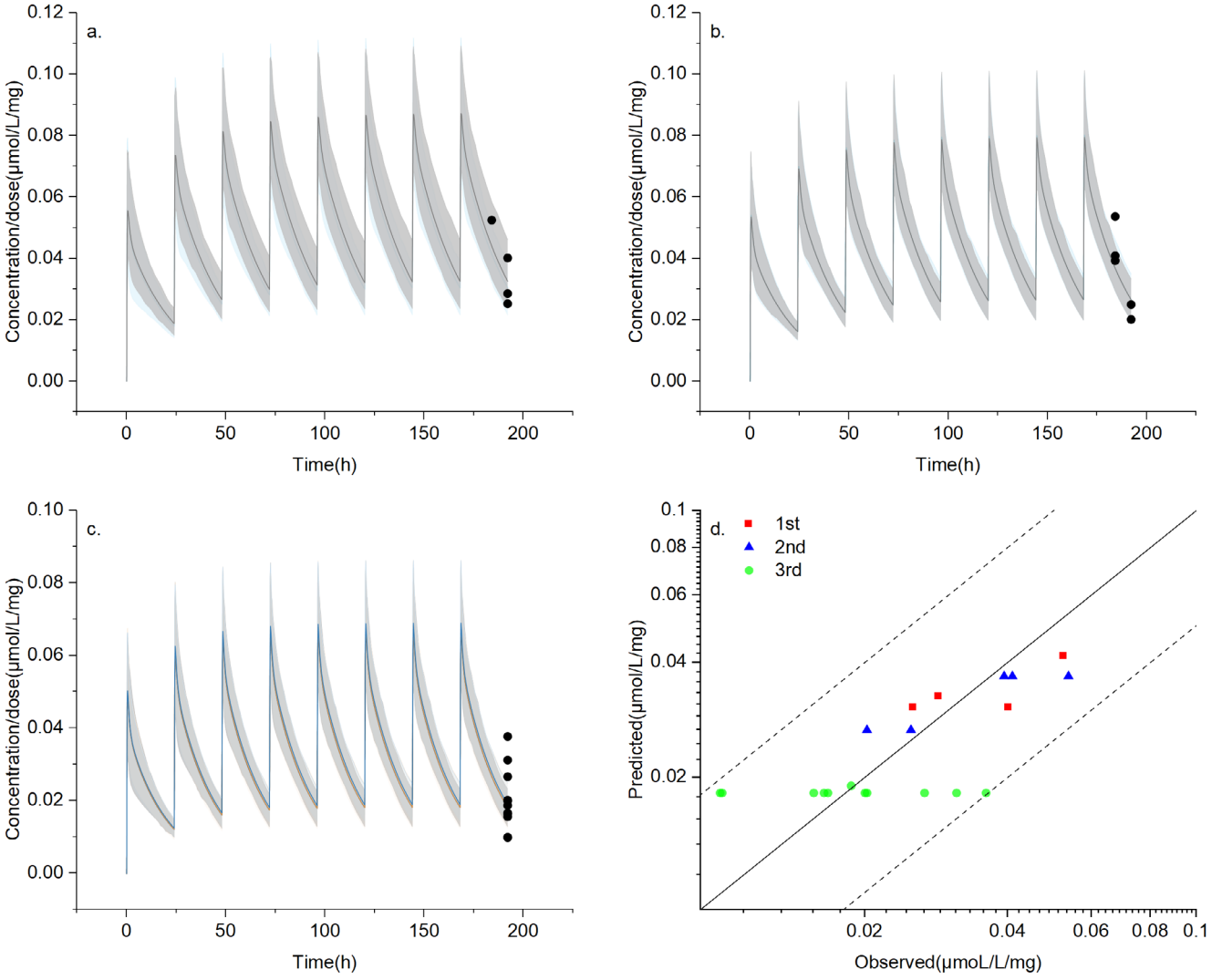

FIGURE 3 | Predicted dose-normalized concentration–time profiles for lamotrigine in pregnant women at different gestational periods. (a) Early pregnancy; (b) mid pregnancy; (c) late pregnancy; (d) goodness-of-fit plot. Dotted line, two-fold error range; closed circles, triangles, and squares, clinical observations of lamotrigine; shaded area, 5%–95% range.

TABLE 1 | Predicted PK parameters of different oral doses of lamotrigine during pregnancy.

Dose	Trimester	$AUC_{0\text{-inf}}$ (μmol min/L)	AUCR	CL (mL/min/kg)	CLR	$C_{max,ss}$ (μmol/L)	$CR_{max,ss}$	$C_{min,ss}$ (μmol/L)	$CR_{min,ss}$
100 mg qd	Non-pregnancy	33990.14		0.51		15.1		7.72	
	1st trimester	11914.67	0.35	0.89	1.75	8.43	0.56	3.01	0.39
	2nd trimester	10837.78	0.32	0.91	1.78	7.95	0.53	2.73	0.35
	3rd trimester	6983.07	0.21	1.16	2.27	6.71	0.44	1.74	0.23
200 mg qd	Non-pregnancy	69802.40		0.50		30.55		15.77	
	1st trimester	24714.96	0.35	0.87	1.74	17.53	0.57	6.23	0.40
	2nd trimester	21750.79	0.31	0.90	1.80	15.87	0.52	5.49	0.35
	3rd trimester	14628.48	0.21	1.12	2.24	13.35	0.44	3.65	0.23
300 mg qd	Non-pregnancy	107422.95		0.50		46.33		24.13	
	1st trimester	37720.70	0.35	0.85	1.70	26.39	0.57	9.54	0.40
	2nd trimester	32965.78	0.31	0.90	1.80	24.52	0.53	8.34	0.35
	3rd trimester	21046.26	0.20	1.15	2.30	20.10	0.43	5.24	0.22
400 mg qd	Non-pregnancy	146852.84		0.50		62.43		32.81	
	1st trimester	51040.64	0.35	0.85	1.70	35.27	0.56	12.89	0.39
	2nd trimester	44006.89	0.30	0.91	1.80	31.57	0.51	11.11	0.34
	3rd trimester	28580.38	0.19	1.16	2.32	26.04	0.42	7.15	0.22
500 mg qd	Non-pregnancy	188092.53		0.49		78.84		41.78	
	1st trimester	64214.3	0.34	0.86	1.76	43.59	0.55	16.2	0.39
	2nd trimester	54770.07	0.29	0.91	1.86	40.04	0.51	13.84	0.33
	3rd trimester	37165.47	0.20	1.12	2.29	33.97	0.43	9.3	0.22
600 mg qd	Non-pregnancy	231157.75		0.49		95.56		51.05	
	1st trimester	75867.05	0.33	0.83	1.69	52.87	0.55	19.2	0.38
	2nd trimester	69365.01	0.30	0.88	1.80	49.14	0.51	17.5	0.34
	3rd trimester	45392.94	0.20	1.14	2.33	40.37	0.42	11.38	0.22
700 mg qd	Non-pregnancy	276074.65		0.49		112.57		60.62	
	1st trimester	93714.37	0.34	0.83	1.69	62.82	0.56	23.68	0.39
	2nd trimester	80376.94	0.29	0.88	1.80	56.54	0.50	20.32	0.34
	3rd trimester	50418.36	0.18	1.14	2.33	47.05	0.42	12.58	0.21
50 mg bid	Non-pregnancy	29414.91		1.03		12.66		9.02	
	1st trimester	9917.31	0.34	1.77	1.72	6.86	0.54	3.99	0.44
	2nd trimester	8079.61	0.27	1.89	1.83	6.15	0.49	3.37	0.37
	3rd trimester	5428.79	0.18	2.29	2.22	5.21	0.41	2.47	0.27
100 mg bid	Non-pregnancy	60395.07		1.02		25.66		18.35	
	1st trimester	20350.81	0.34	1.75	1.72	13.64	0.53	8.14	0.44
	2nd trimester	17094.34	0.28	1.90	1.86	11.84	0.46	6.88	0.37
	3rd trimester	11246.37	0.19	2.30	2.25	9.86	0.38	5	0.27

(Continues)

TABLE 1 | (Continued)

Dose	Trimester	$AUC_{0\text{-inf}}$ (μmol min/L)	AUCR	CL (mL/min/kg)	CLR	$C_{max,ss}$ (μmol/L)	$CR_{max,ss}$	$C_{min,ss}$ (μmol/L)	$CR_{min,ss}$
150 mg bid	Non-pregnancy	92946.95		1.02		38.99		28	
	1st trimester	30858.81	0.33	1.74	1.71	20.63	0.53	12.33	0.44
	2nd trimester	26545.62	0.29	1.85	1.81	18.27	0.47	10.68	0.38
	3rd trimester	16603.52	0.18	2.31	2.26	14.67	0.38	7.46	0.27
200 mg bid	Non-pregnancy	127063.16		1.01		52.63		37.95	
	1st trimester	41294.93	0.32	1.73	1.71	27.77	0.53	16.63	0.44
	2nd trimester	35,452	0.28	1.84	1.82	24.93	0.47	14.37	0.38
	3rd trimester	22939.08	0.18	2.32	2.30	19.35	0.37	10.06	0.27
250 mg bid	Non-pregnancy	162761.3		1.01		66.58		48.19	
	1st trimester	52664.82	0.32	1.74	1.72	34.76	0.52	20.92	0.43
	2nd trimester	44963.29	0.28	1.82	1.80	31.66	0.48	18.19	0.38
	3rd trimester	28350.34	0.17	2.30	2.28	24.75	0.37	12.63	0.26
300 mg bid	Non-pregnancy	200049.08		1.00		80.84		58.71	
	1st trimester	62680.07	0.31	1.75	1.75	41.67	0.52	24.99	0.43
	2nd trimester	55132.83	0.28	1.84	1.84	36.68	0.45	21.88	0.37
	3rd trimester	34812.78	0.17	2.33	2.33	29.81	0.37	15.22	0.26
350 mg bid	Non-pregnancy	238944.31		1.00		95.39		69.51	
	1st trimester	73991.13	0.31	1.75	1.75	48.52	0.51	29.31	0.42
	2nd trimester	61638.81	0.26	1.82	1.82	43.56	0.46	25.43	0.37
	3rd trimester	42545.26	0.18	2.26	2.26	35.16	0.37	18.46	0.27

Note: $AUC_{0\text{-inf}}$, area under the concentration-time curve; $AUCR = AUC_P / AUC_N$, where AUC_P is pregnant population, AUC_N is non-pregnant population; CL, clearance; $CLR = CL_P / CL_N$, where CL_P and CL_N represent the apparent clearance in pregnant population and in non-pregnant population, respectively; $C_{max,ss}$, maximum steady-state plasma drug concentration during a dosage interval; $CR_{max,ss} = C_{max,ss,P} / C_{max,ss,N}$, where $C_{max,ss,P}$ and $C_{max,ss,N}$ represent the steady-state peak plasma concentrations in pregnant population and in non-pregnant population, respectively; $C_{min,ss}$, minimum steady-state plasma drug concentration during a dosage interval; $CR_{min,ss} = C_{min,ss,P} / C_{min,ss,N}$, where $C_{min,ss,P}$ and $C_{min,ss,N}$ represent the steady-state trough plasma concentrations in pregnant population and in non-pregnant population, respectively; bid, twice a day; qd, once a day.

respectively. The results showed that the fetal umbilical vein blood concentrations predicted by the isolated cotyledon perfusion method were more similar to the observed fetal umbilical vein blood concentrations (Figure 5), with fold error ranging from 0.67 to 1.46 (Table S8), which were closer to 1 than the other two approaches. Accordingly, the isolated cotyledon perfusion method was considered suitable for predicting lamotrigine fetal PK. Additionally, the maternal concentration–time curves of different doses were added. The fetal umbilical vein and maternal concentrations were compared to give a mean C_f/C_m value of 1.49.

3.4 | Dosage Recommendation for Pregnancy

Compared with non-pregnancy, exposure was approximately 30% in early and mid-pregnancy and 20% in late pregnancy following 100–700 mg daily lamotrigine regimens (Table 1). Therefore, three, three, and five times the baseline lamotrigine dose are recommended to reduce seizures in early, mid, and late pregnancy, respectively.

However, considering fetal safety, a fetal risk concentration (4.87 mg/L) was used to limit the daily dose [14]. Fetal PK profiles at different doses and stages of pregnancy were simulated using the permeability parameters obtained with the isolated cotyledon perfusion method, ensuring that the $C_{min,ss}$ in the simulated fetal PK curve did not exceed the fetal risk concentration to ensure fetal safety. The results suggest that for once-daily administration, the daily dose should not exceed 400, 500, and 700 mg in early, mid, and late pregnancy, respectively (Figure 6a–c). Similarly, the twice-daily dose should not exceed 300, 400, and 600 mg in early, mid, and late pregnancy, respectively (Figure 6d–f). Of note, due to the current scarcity of maternal–fetal data, the above dosage recommendations are preliminary, warranting more robust data to further inform dosing schemes.

4 | Discussion

Physiological changes in women during pregnancy alter the PK of ASMs, increasing the frequency of seizures and endangering

the lives of the pregnant woman and fetus. However, gaps in our clinical understanding of lamotrigine maternal–fetal PK and dose adjustment have caused inadequate management of lamotrigine during pregnancies. This study presents the first PBPK model to simultaneously explore lamotrigine maternal–fetal PK during pregnancy and provides recommendations for dose adjustments to control seizures and ensure fetal safety with precision medication in pregnancy.

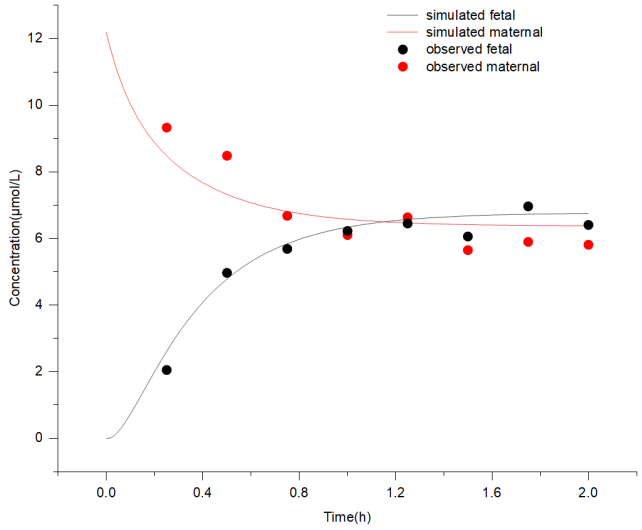

FIGURE 4 | Comparison of observed and simulated concentrations of fetal and maternal lamotrigine by ex vivo cotyledon perfusion. Black line, simulated fetal curve; red line, simulated maternal curve; black closed circles, fetal clinical observations of lamotrigine; red closed circles, maternal clinical observations of lamotrigine.

A recent study found that exposure to lamotrigine is reduced during pregnancy [47], and our findings further support this conclusion and also inform the changes in lamotrigine maternal PK during pregnancy. However, there are two main innovations of the current study compared to the previous study. First, Costa et al. only established a maternal model, whereas the current study developed a maternal and fetal model, investigating the PK behavior of lamotrigine in both during pregnancy. Second, Costa et al. only modeled specific doses at particular gestational ages (GAs) (150 mg at 10 GA, 200 mg at 20 GA, 400 mg at 30 GA, and 300 mg at 40 GA) without providing a dose recommendation protocol. In contrast, the current study made dose recommendations for different gestational stages based on the simulation results of the maternal model and set the maximum upper limit of the recommended dose for each gestational stage based on the fetal model regarding fetal safety. This ensured maternal seizure control and fetal safety during pregnancy.

Changes in the activity of UGT1A3 during pregnancy have not been previously reported. However, lamotrigine is primarily metabolized by UGT1A4 and secondarily by UGT1A3 [48]. Therefore, UGT1A3 activity was hypothesized to remain relatively unchanged during pregnancy. Based on a previous study [22], the enzyme activity of UGT1A4 was amplified by 1.79-, 1.9-, and 2.47-fold in pregnant women during early, mid, and late pregnancy compared with that in non-pregnancy, respectively

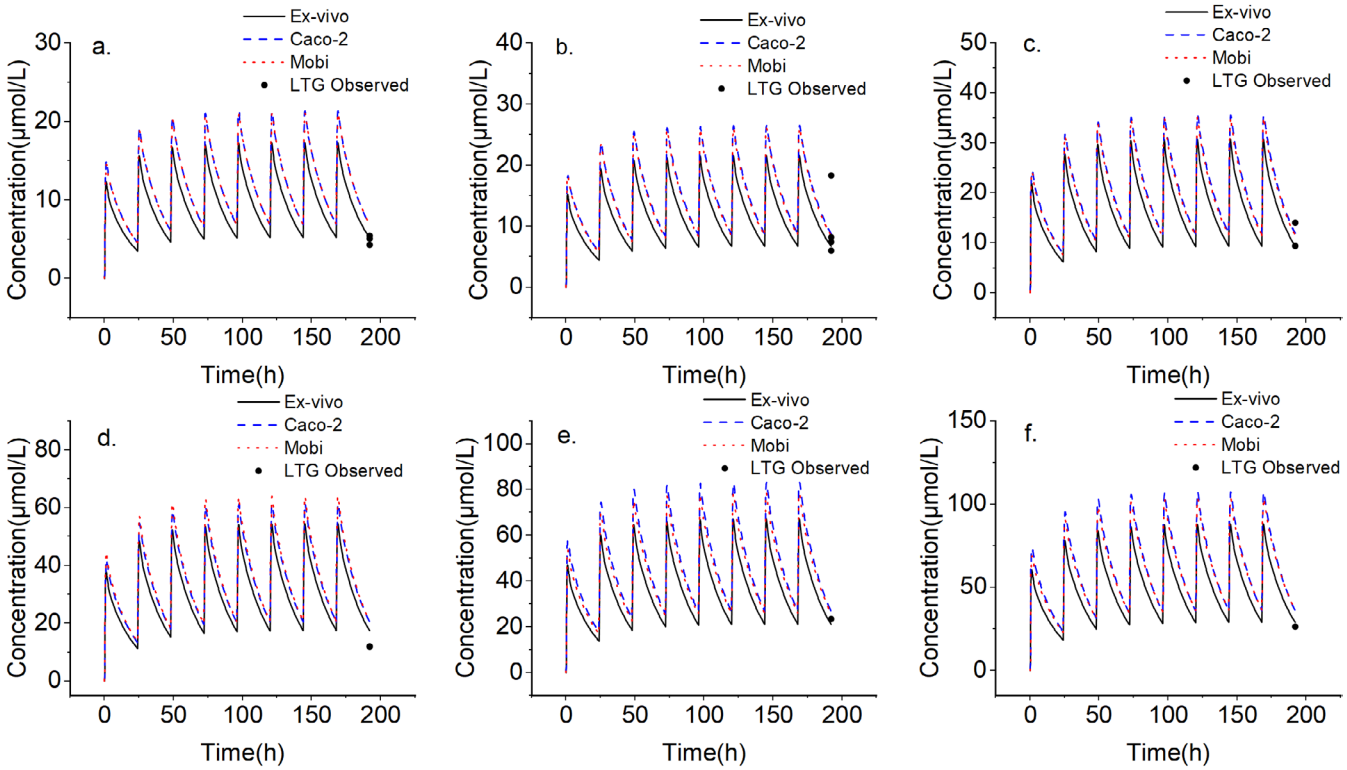

FIGURE 5 | Three methods for predicting the concentration–time profiles of the fetal umbilical vein following maternal administration of various doses of lamotrigine. (a) Oral 200 mg/d; (b) oral 250 mg/d; (c) oral 350 mg/d; (d) oral 600 mg/d; (e) oral 750 mg/d; (f) oral 1000 mg/d. Solid black line, fetal umbilical vein predicted concentration–time curves using the isolated cotyledon perfusion method; blue dotted line, Caco-2 cell permeability method; red dotted line, MoBi default method; black closed circles, fetal clinical umbilical cord blood observations of lamotrigine; d, day.

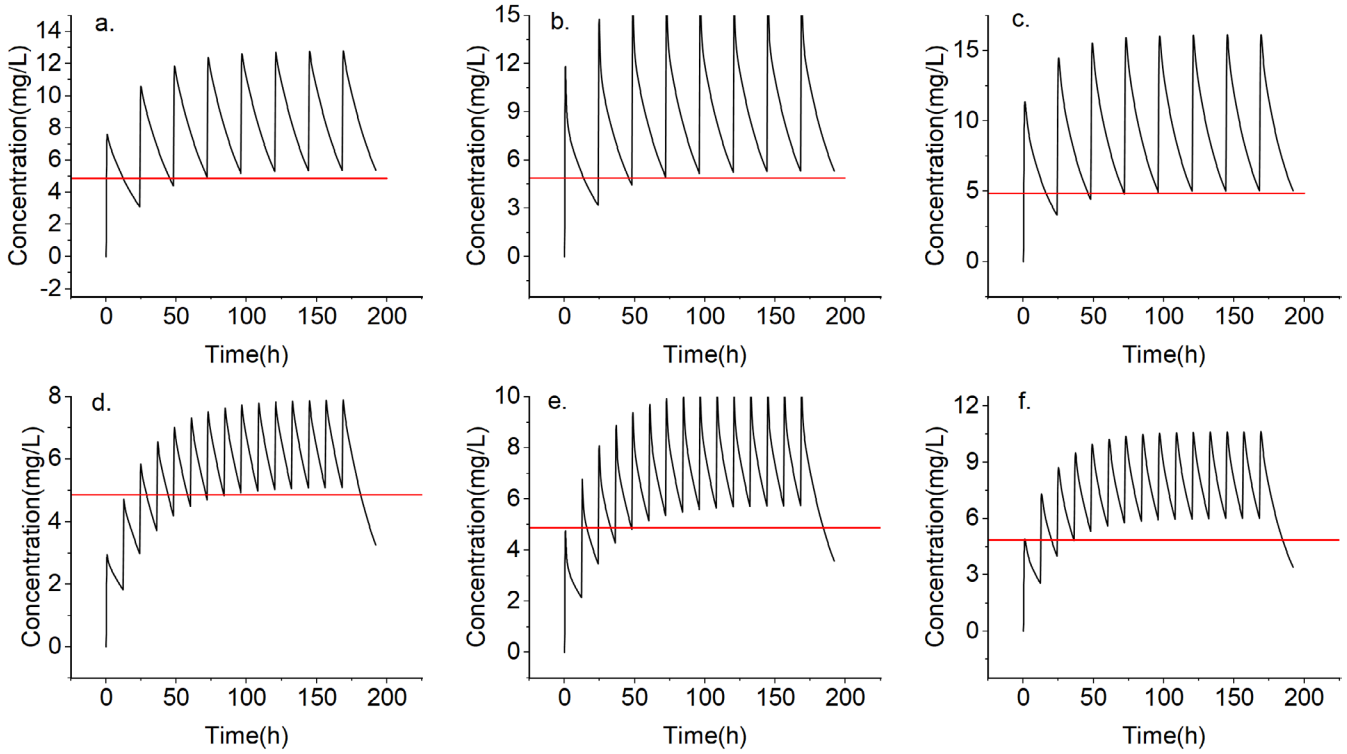

FIGURE 6 | Fetal PK curves after maternal administration of different doses of lamotrigine during early, mid and late pregnancy. (a) Oral 400 mg qd in early pregnancy; (b) oral 500 mg qd in mid-pregnancy; (c) oral 700 mg qd in late pregnancy; (d) oral 150 mg bid in early pregnancy; (e) oral 200 mg bid in mid-pregnancy; (f) oral 300 mg bid in late pregnancy. Black solid line, predicted fetal PK profile; red dashed line, risk concentration of fetus (4.87 mg/L); bid, twice daily; qd, once daily.

(Table S2). Our study revealed that the lamotrigine CL increased by 72.9%, 81.9%, and 128.3%, and the AUC decreased by 66.5%, 71.1%, and 81.2% during early, mid, and late pregnancy compared to that in non-pregnancy, respectively. This suggests that changes in UGT1A4 activity are closely related to changes in lamotrigine CL and exposure.

The PK of lamotrigine in pregnant women was predicted using the PBPK model; AUC and $C_{min,ss}$ decreased significantly, whereas CL increased significantly during pregnancy (Table 1). Predicted gestational CL increased by 72.9%–128.3% during pregnancy, which aligns with the 65%–248% increase in CL compared to non-pregnancy that has been reported by others [13, 49]. Furthermore, as drug efficacy is most closely related to the AUC, based on our findings, the dose should be increased by three-, three-, and five-fold in early, mid, and late pregnancy, respectively, to achieve effective exposure and control seizures, compared with that during non-pregnancy. This is consistent with the results of a previous study in which the dose of lamotrigine was increased by three-fold on average during pregnancy compared with non-pregnancy [13]. If seizure control is not achieved after increasing the lamotrigine dose, it is recommended to add other ASMs rather than further increasing the dosage to ensure safety.

Three methods were used to predict the D_{cot} and $K_{f,m}$ values during placental transfer and then incorporated into the fetal PBPK model to select the most appropriate method (Figure 5). The fetal concentrations predicted using the isolated cotyledon perfusion method were closer to the observed fetal umbilical vein concentrations at delivery than those of the other methods. Moreover, PBPK model-predicted C_f/C_m for lamotrigine (1.49) was within the range (0.56–1.55) reported in the literature [13] and greater than 1. This further demonstrates the reliability of the fetal lamotrigine model and confirms that lamotrigine can be widely transferred via the placenta. Moreover, the predicted C_f/C_m value partly explains the phenomenon of lamotrigine concentrations in the fetus exceeding those in the mother during the later stages of placental perfusion.

This study used a reliable fetal model to consider the fetal risk concentration (4.87 mg/L). It was then combined with a maternal model to control seizures in mothers and ensure fetal safety. In addition, serum lamotrigine concentrations have been demonstrated to quickly return to pre-pregnancy levels within a few days of delivery and to return completely 2–3 weeks postpartum [50], suggesting that a gradual dose reduction after delivery is needed to avoid toxic reactions.

This study has several limitations. First, it did not consider polymorphisms in the lamotrigine metabolizing enzyme UGT1A4 and genetic variability during pregnancy. Second, there is a lack of clinically available data regarding lamotrigine use in pregnant women and fetuses due to ethical considerations. Moreover, the model assessment may be restricted as it relies solely on steady-state trough concentrations for validation. Thus, future studies should collect the full PK profiles to validate this model. Given the scarcity of available clinical data, this model could be used to support dose selection, which would require confirmation in a clinical setting before adjusting doses.

In conclusion, this study describes the maternal and fetal PK changes in lamotrigine during pregnancy, which can better predict maternal and fetal exposure and deepens the understanding of lamotrigine during pregnancy. Simulation results showed that plasma lamotrigine concentrations substantially decrease during pregnancy, requiring dose adjustments to control seizures and ensure fetal safety. This study provides information for clinical decision-making regarding the use of lamotrigine during pregnancy with simultaneous maternal and fetal consideration.

Author Contributions

Y.Q., W.W., and W.L. wrote the manuscript; W.L. designed the research; Y.Q., W.W., C.K., and X.G. performed the research; Y.Q., S.L., J.C., and Y.C. analyzed the data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All the data in this paper will be made available upon request to the corresponding author (lww13705063157@163.com).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.