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Pregnancy induces physiological changes that can alter drug metabolism, particularly via CYP450 and UGT pathways, increasing the risk of drug-drug interactions (DDIs) [1]. Lamotrigine (LTG), used for epilepsy and bipolar disorder, shows reduced plasma levels during pregnancy due to increased UGT1A4 activity [2]. Efavirenz (EFV), an antiretroviral metabolized mainly by CYP2B6 and partly by UGTs, is also affected by pregnancy and genetic variations [3]. Co-administration of LTG and EFV during pregnancy raises concerns about altered drug exposure and treatment failure. PBPK and pregnancy-specific PBPK (p-PBPK) models for LTG and EFV were developed based on literature-derived parameters [4,5] and GastroPlus® standard files [6], respectively, to assess UGT-mediated DDI risk and inform safe, effective dosing during pregnancy [7]

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graph TD
    A[Clinical PK Data Collection] --> B[Development of adult PBPK model  
For LTG and EFV]
    B --> C[Pregnancy model adaptation  
For LTG and EFV]
    C --> D[Dose Simulation  
# trimester]
    D --> E[Model Evaluation and Validation  
(with literature data)]
    E --> F[Drug-drug interaction  
(DDI simulation)]
    F --> B
    F --> C
    F --> D
    F --> E
    
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The flowchart illustrates the iterative process of developing and validating a pregnancy PBPK model. It begins with **Clinical PK Data Collection**, leading to the **Development of adult PBPK model** for LTG and EFV. This model is then adapted for **Pregnancy** (also for LTG and EFV). The process continues to **Dose Simulation** (accounting for the number of trimesters) and **Model Evaluation and Validation** (using literature data). A **Drug-drug interaction (DDI) simulation** is performed, which feeds back into the development and adaptation stages, as well as the simulation and evaluation stages, indicating an iterative refinement process.

Table 1. LTG, enzyme table, and fm values for steady-state DDI predictions non-pregnant. The Vmax and Km values for non-pregnant individuals were collected from the literature [8]. For the different gestational weeks (10–40 weeks), the DDI module computed a Clint value ($Cl_{int} = V_{max}/K_m$).

Pregnant/Gestational Week	Enzyme	Vmax (mg/s/mg-Enzyme)	Km (μg/mL)	Clint (L/h)	fm (%)	Turnover (l /min)
Non-pregnant	UGT1A3	0.0000681	18.83	0.3411	8.63	-
	UGT1A4	0.00466	147.95	3.1564	79.90	-
10 weeks	UGT1A3	-	-	2.99×10^{-1}	8.5	0.0005
	UGT1A4	-	-	2.77	78.65	0.0005
20 weeks	UGT1A3	-	-	2.88×10^{-1}	8.46	0.0005
	UGT1A4	-	-	2.67	78.28	0.0005
30 weeks	UGT1A3	-	-	2.74×10^{-1}	8.4	0.0005
	UGT1A4	-	-	2.53	77.73	0.0005
40 weeks	UGT1A3	-	-	2.61×10^{-1}	8.34	0.0005
	UGT1A4	-	-	2.41	77.2	0.0005

Table 2. Enzyme EFV and preparator steady state DDI predictions. EFV as a moderate CYP3A4 inducer for DDI predictions using available induction parameters and observations.

Enzyme	CYP2B6	CYP3A4	UGT1A4	UGT1A9
Vmax (mg/s/mg-enzyme)	0.050 (PBPK)	0.000562 (PBPK), 0.2 (Gut)	0.0000208 (PBPK), 0.0583 (Liver)	0.000111 (PBPK), 0.0091 (Liver)
Km (µg/mL)	3.137	3.137	0.069	0.0051
Inh/Ind Const Value (µM)	0.82	1	2	9.4
Inh/Ind Const Type	EC50-in vitro, T (induction)	EC50-in vitro, T	Ki-rev-in vitro T	Ki-rev-in vitro T
E _{max}	5.76	9.9	-	-
In vitro F _u	0.063	0.063	0.12	0.12
In vitro F _u Type	User	User	Calc(Austin)-HLM	Calc(Austin)-HLM
In vitro Prot Conc (mg/mL)	0	0	0.5	0.5
Ref	GastroPlus model standard	GastroPlus model standard	[ref]	[ref]

These published findings leveraged PBPK and pregnancy-specific PBPK (p-PBPK) models **incorporating literature-based Vmax and Km values** to simulate the pharmacokinetics and interaction of lamotrigine (LTG) and efavirenz (EFV) during pregnancy. – Co-administration of EFV led to a slight, **clinically insignificant increase in LTG exposure across all gestational ages**, indicating no need for LTG dose adjustments. The LTG model reliably captured pregnancy-related reductions in exposure. In contrast, the EFV model showed limited predictive accuracy, suggesting the need for further refinement to address its complex metabolism during pregnancy.

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Table 3. Model validation results: pharmacokinetic parameters predicted (Pred) and observed (Obs) for oral administration of lamotrigine (LTG) and efavirenz (EFV) in adults, for different doses. If %PE <25%, we considered it as actually supporting personalized dosing

Drug	Dose	Dosage Form/ Protocol	AUC 0– t (ug/mL-h)			Cmax ug/mL			Tmax (h)		
LTG			Pred	Obs	%PE	Pred	Obs	%PE	Pred	Obs	%PE
	25 mg - Ebert et al. [9]	Oral/SD	8.42	7.9	6.64	0.31	0.26	18.27	1.6	2.65	–39.62
	75 mg - Peck et al. [10]	Oral/SD	25.85	23.30	10.92	1.03	0.883	17.11	1.1	2.108	–47.82
	100 mg - van Luin et al. [11]	Oral/SD	33.81	33.8	0.07	1.37	1.13	20.89	1.14	2.13	–47.8
	200 mg – Inceciayir et al. [12]	Oral/SD	91.56	106.91	–14.35	2.75	2.84	–3.13	1.1	1.77	–37.99
	200 mg – Wootton et al. [13]	Oral/SD	93.001	89.027	4.470	2.74	2.36	16.01	1.1	2.538	–56.66
EFV	400 mg Cerrone et al. [14]	Oral/SD	45.58	52.86	–13.78	3.24	2.98	8.89	-	-	-
	600 mg Villani et al. [15]	Oral/SD	68.99	100.61	–31.42	4.9	6.034	–18.79	1.92	3.034	–36.72

Table 4. Model validation results: pharmacokinetic parameters predicted (Pred) and observed (Obs) for oral administration of lamotrigine (LTG) and efavirenz (EFV) in adults during pregnancy, for different doses.

Drug	Dose and Gestational week	Dosage Form/Protocol	AUC _{0-t} (ug/mL-h)			Cmax ug/mL			Tmax (h)		
			Pred	Obs	%PE	Pred	Obs	%PE	Pred	Obs	%PE
LTG	400 mg / 30 weeks - Reimers et al. [16]	Oral/SD	47.67	43.4	9.84	5.05	5.3	-4.064	1.32	2.3	-42.6
	600 mg / 33weeks - Cressey et al. [17]	Oral/SD	20.77	165.18	-87.4283	2.79	8.33	-66.39	1.36	1.94	-30.04
EFV	600 mg / 23 weeks - Lartey et al. [18]	Oral/SD	22.27	43.00	-48.22	2.99	3.09	-3.22	1.28	3.61	-64.51

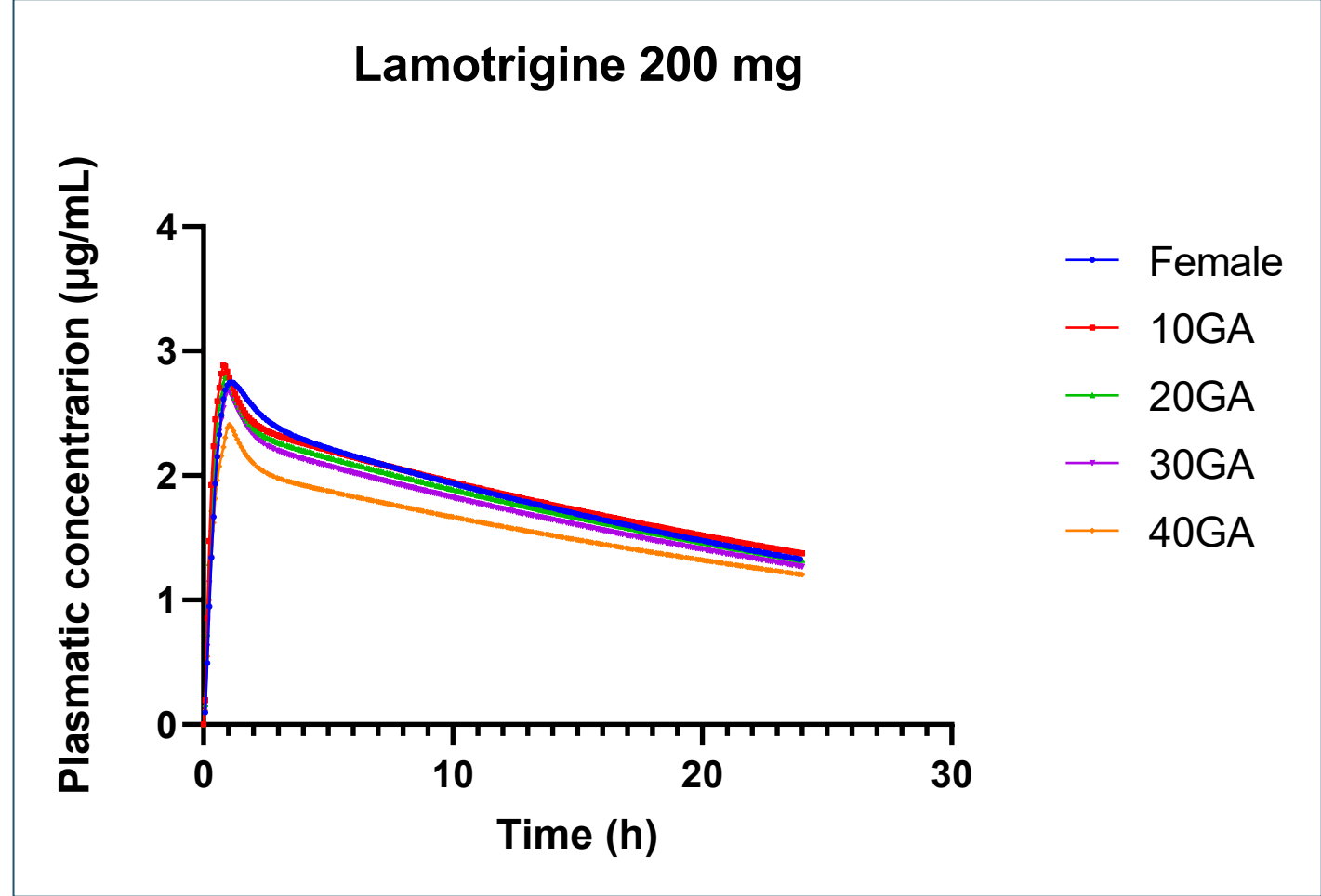


Figure 1. 24-h plasma concentration profiles of 200 mg LTG in healthy female individuals (blue) and for different gestational weeks: 10 (red), 20 (green), 30 (purple), and 40 (orange).

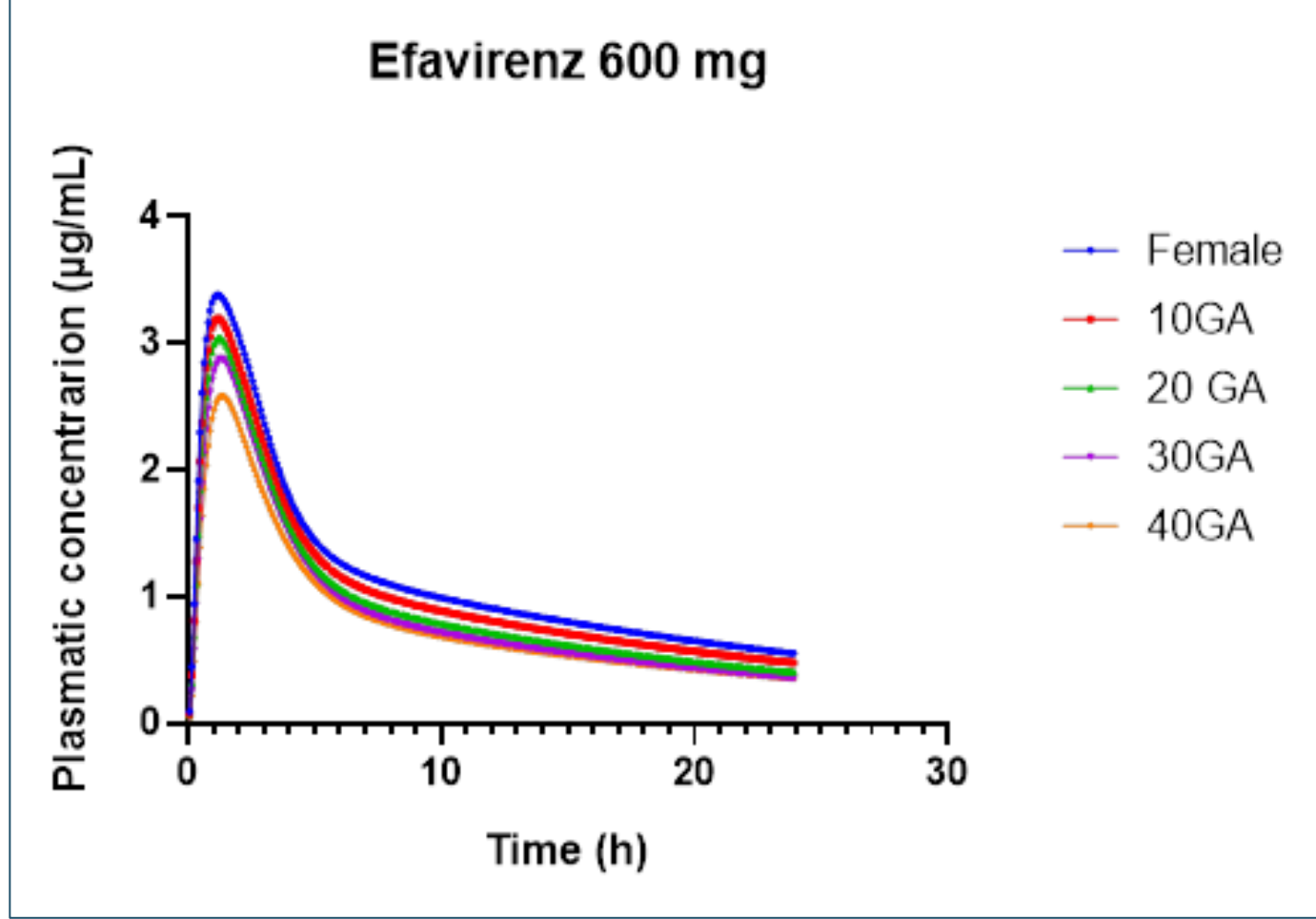


Figure 2. 24-h plasma concentration profiles of 600 mg EFV in healthy female individuals (blue) and for different gestational weeks: 10 (red), 20 (green), 30 (purple), and 40 (orange).

Table 5. The statistical metrics used to evaluate the PBPK models for lamotrigine (LTG) and efavirenz (EFV) in both standard (non-pregnant adult males) and pregnant individuals indicate generally good predictive performance.

Metric	LTG				EFV			
	Standard Cmax	Standard AUC	Pregnancy Cmax	Pregnancy AUC	Standard Cmax	Standard AUC	Pregnancy Cmax	Pregnancy AUC
AFE	1.1423	0.913	0.923	1.098	1.23	1.21	0.28	0.43
AAFE	0.9130	1.0953	1.049	1.098	1.23	1.21	3.44	2.35
MAE	0.35	9.47	0.25	4.3	0.9	11.84	3.13	30.96
RMSE	0.35	9.47	0.25	4.3	0.9	11.84	3.13	30.96

Table 6. Results of the Dynamic Simulation Assessing Drug-Drug Interactions Between LTG and EFV in the Standard PBPK Model, show no clinically significant increase in LTG exposure when combined with EFV

PBPk model	Drug	Fa [%]	FDp [%]	F [%]	Cmax [μg/mL]	Tmax [h]	AUC(0-t) [μg·h/mL]	AUC(0-inf) [μg·h/mL]
Female (100 mg)	LTG	1	1	1.001	1.003	1	0.001009	0.001016
	EFV	1	0.976	0.973	0.991	0.933	0.000953	0.000934
10 GA (150 mg)	LTG	1	1	1.001	1.003	1	0.001009	0.001013
	EFV	1	0.969	0.964	0.988	1	0.000945	0.000925
20 GA (200 mg)	LTG	1	1	1.001	1.004	1	0.001009	0.001013
	EFV	1	0.963	0.958	0.987	0.938	0.000939	0.000923
30 GA (400 mg)	LTG	1	1	1.001	1.004	1	0.001008	0.001016
	EFV	1	0.961	0.955	0.986	0.941	0.000934	0.000919
40 GA (300 mg)	LTG	1	1	1.002	1.004	1	0.001007	0.001007
	EFV	1	0.963	0.956	0.985	1	0.000934	0.000916

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