Supplemental Material

Application of Physiologically Based Pharmacokinetic Modeling to Predict Maternal Pharmacokinetics and Fetal Exposure to Oxcarbazepine

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TableS1. List of reported clinical studies in pregnancy that were used for modeling.

reference	Patient Population Number	weight(kg)	age(year)	Trimester	Dose(mg)
Mazzucchelli,I.et al.[1]	PG:5	54-62	22-34	P1;P2;P3	150-1500mg/d
Yin,X.et al.[2]	PG:56 WWE:53	NR	NR	P1;P2;P3	600-1050mg/d

NP = non-pregnant; P1 = first trimester; P2 = second trimester; P3 = third trimester; PG = pregnant;WWE: women with epilepsy.

Table S2. The expression concentrations of UGT1A9 and UGT2B7 during different periods, across organs and tissues (mainly), and the difference in renal blood flow between nonpregnant and pregnant women.

enzymes	UGT1A9(μmol/l)			UGT2B7(μmol/l)
	Kidey-intracellular	Kidey-tissue	liver periportal -intracellular	liver periportal -intracellular
nonpregnancy	1.77		0.15	1.71
1st trimester	1.78	1.32	0.15	1.7
2nd trimester	1.77	1.32	0.15	1.68
3rd trimester	1.78	1.32	0.15	1.64
renal clearances	plasma clearance(ml/min/kg)			
nonpregnancy	0.27			
1st trimester	5			
2nd trimester	5			
3rd trimester	5			

Supplementary Workflow Figures:

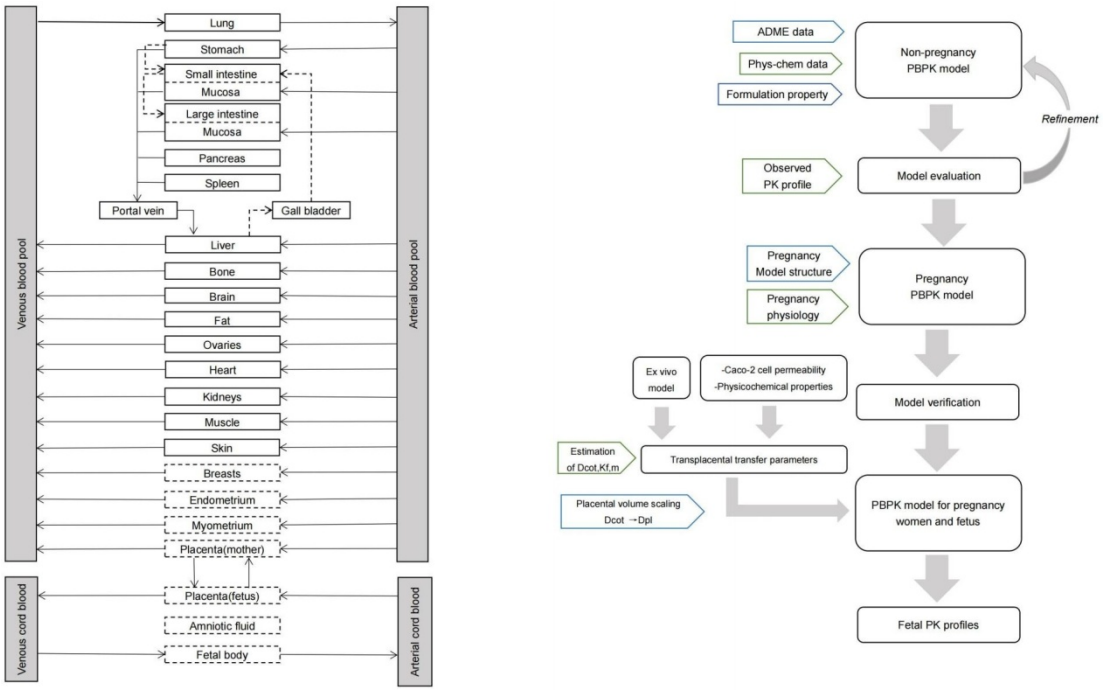


Figure S1. Structure of the pregnancy PBPK model and fetal-maternal physiologically based pharmacokinetic (f-m PBPK) model. On the left is the structure of the pregnancy PBPK model. Thick arrows indicate drug transport through blood flow, and thin arrows indicate drug transport through other routes (e.g., gastrointestinal passages, biliary excretion through the gallbladder, and diffusive transfer within the placenta). Compartments that only belong to the structure of the pregnancy PBPK model are shown in italics, with dashed borders and dashed arrows indicating drug transfer through the bloodstream. On the right is a schematic representation of the work in development and evaluation of the f-m PBPK model.[3-5]D_{cot}, transcotyledon passive diffusion clearance; D_{pl}, passive fusion clearance through placenta; $K_{f,m}$, partition between fetal and maternal compartments; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics.

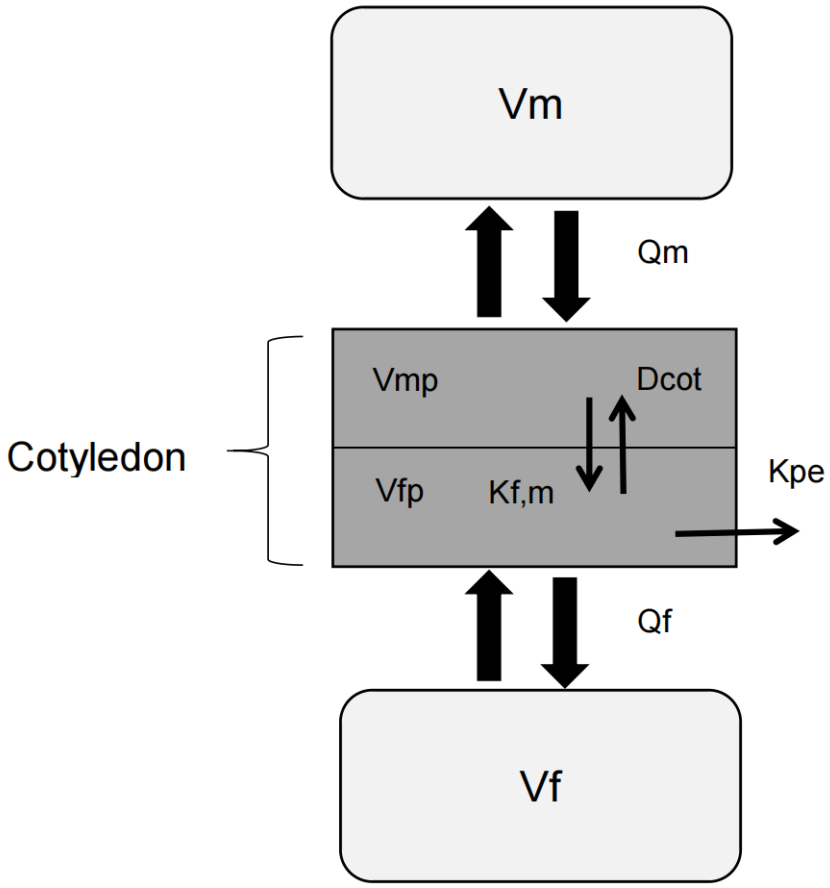


Figure S2. Schematic representation of the ex vivo cotyledon perfusion model.[6-7]

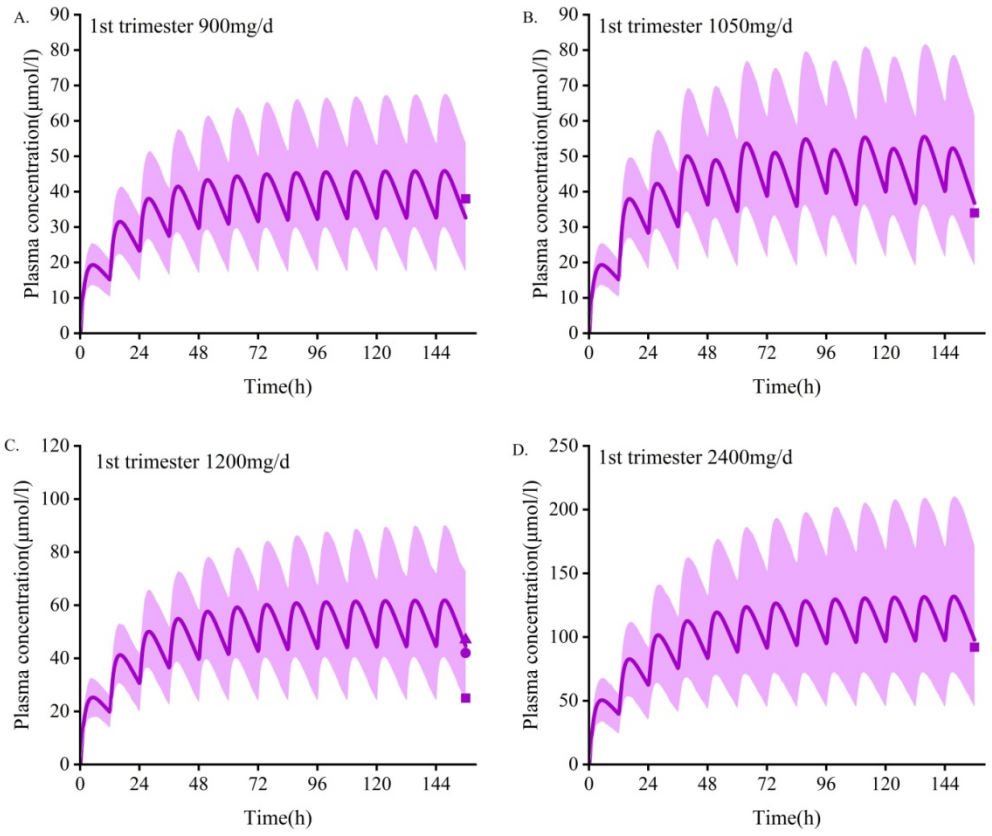


Figure S3. Median plasma concentration of the population taking different doses of OXC in the first trimester of pregnancy predicted by population PBPK simulation (A–D) is shown as a dark line, and the shaded area represents the 5th to 95th prediction range. OXC, oxcarbazepine.

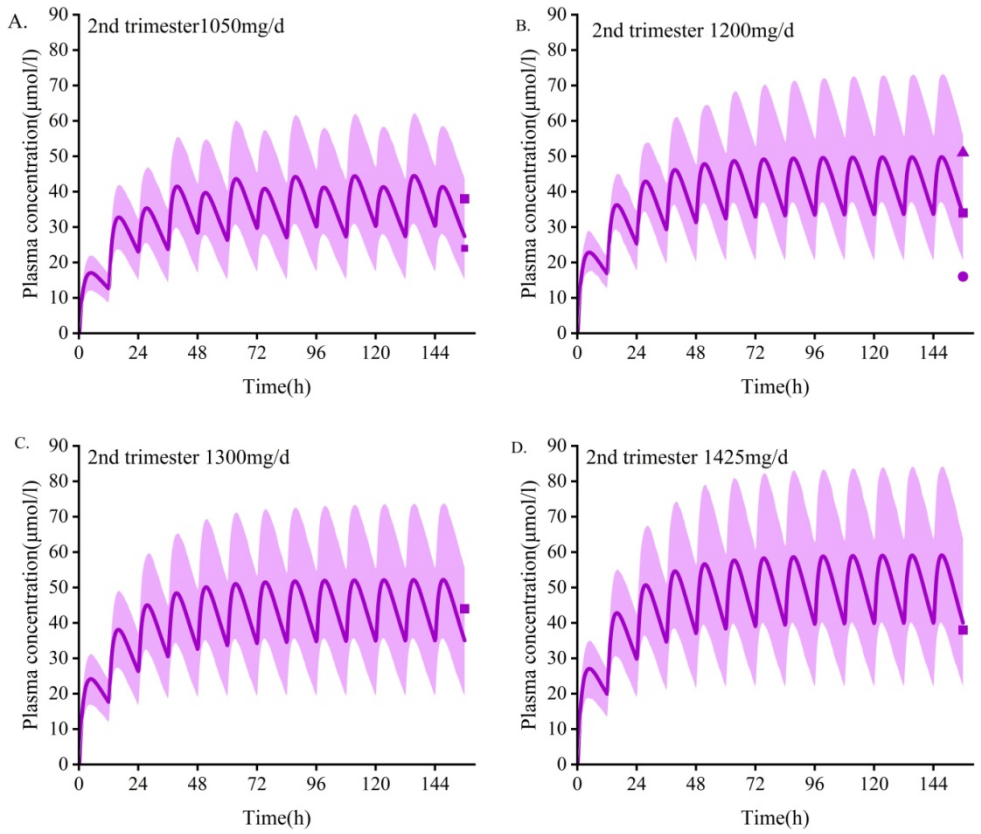


Figure S4. Median plasma concentration of the population taking different doses of OXC in the second trimester of pregnancy predicted by population PBPK simulation (A–D) is shown as a dark line, and the shaded area represents the 5th to 95th prediction range.

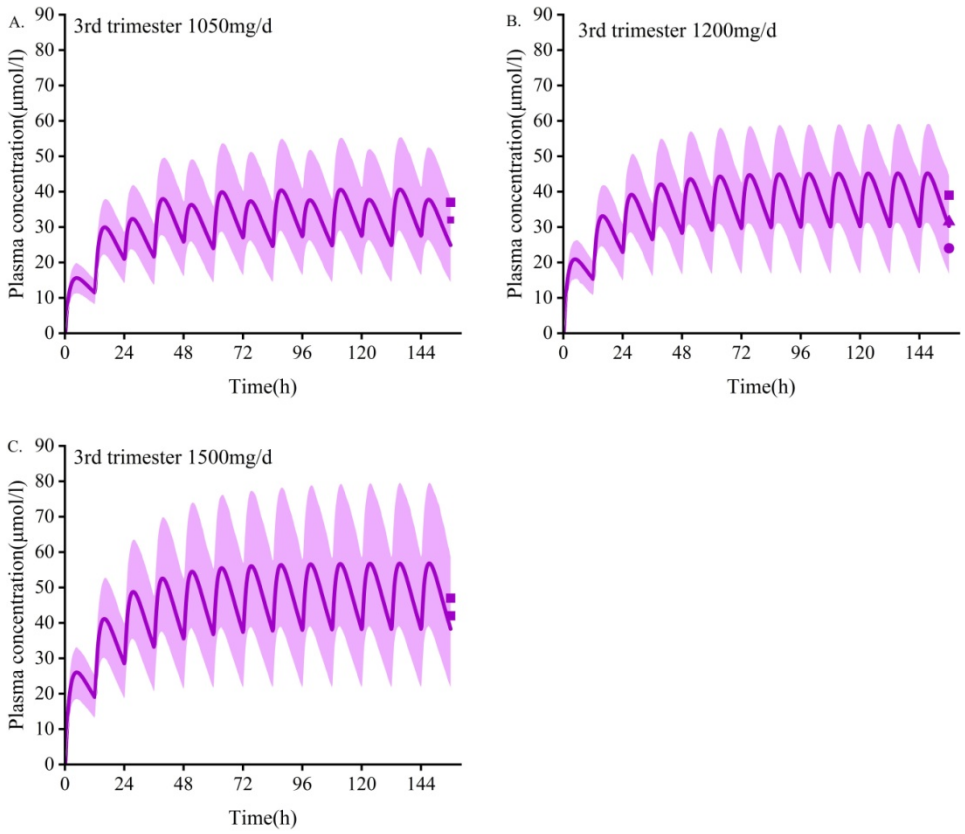


Figure S5. Median plasma concentration of the population taking different doses of OXC in the third trimester of pregnancy predicted by population PBPK simulation (A–C) is shown as a dark line, and the shaded area represents the 5th to 95th prediction range.

References

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