

Prediction of human foetal pharmacokinetic profile using transplacental parameters from ex-vivo human placenta perfusion model and pregnancy-PBPK models



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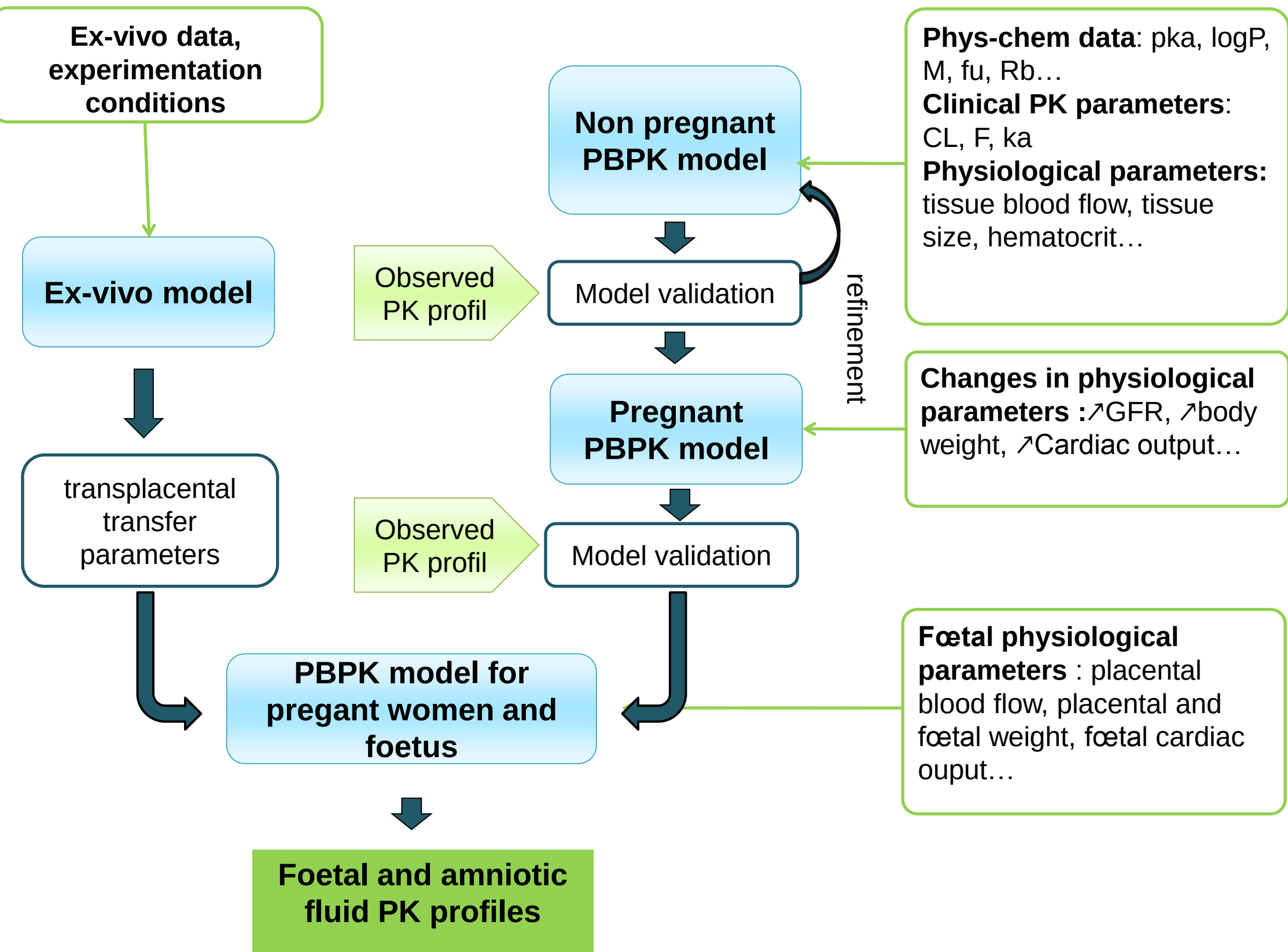
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INTRODUCTION

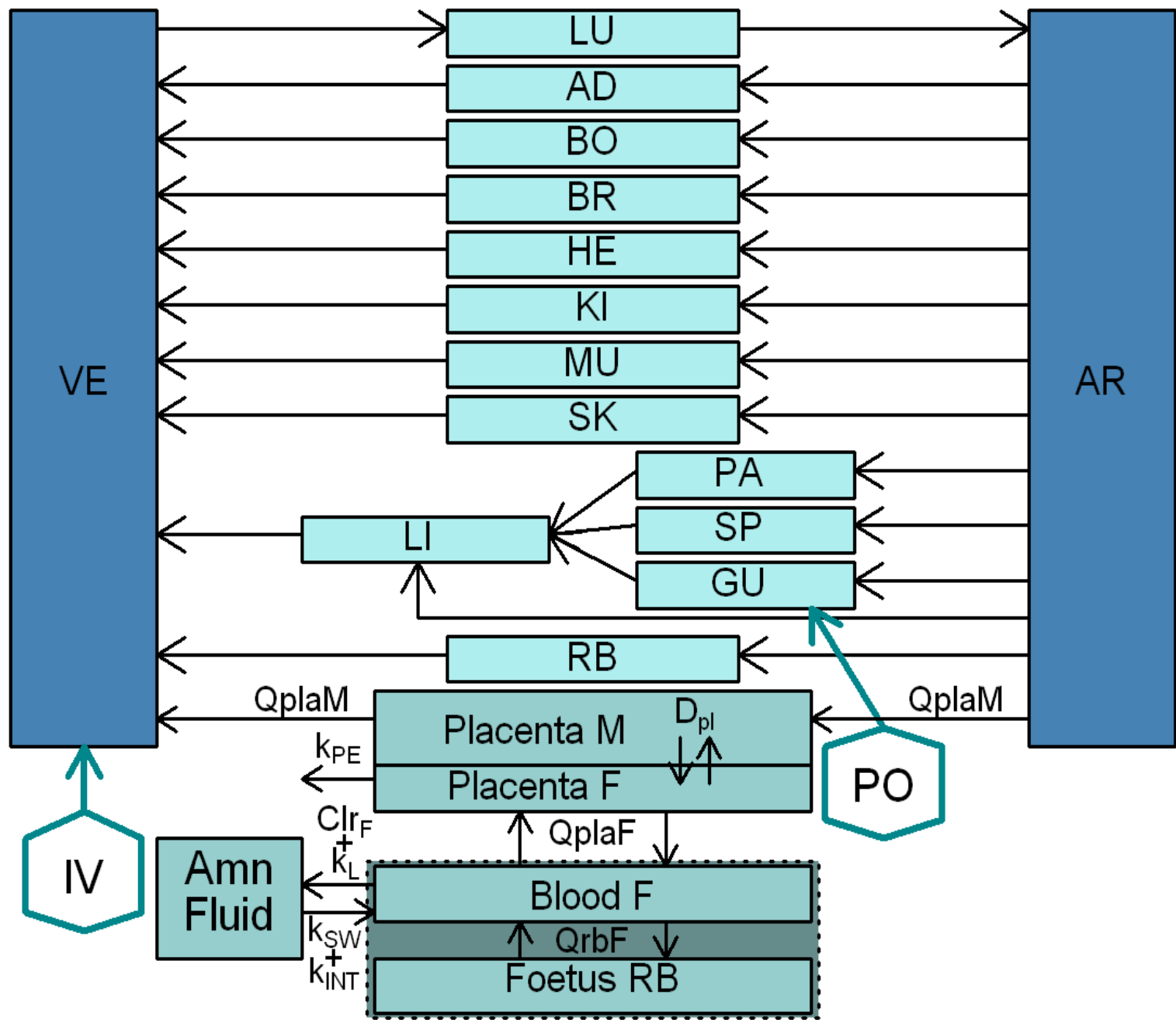
Pregnant women can be exposed to numerous drugs during the gestational period. Due to obvious ethical reasons, in vivo studies of foetal exposure to drugs are limited. Moreover information about drug transplacental transfer prior administration to pregnant women would be highly useful. A novel approach is developed to quantitatively predict foetal exposure to drugs administered to the mother.

METHODS



We implemented transplacental parameters values estimated from the ex-vivo human placenta perfusion model in pregnancy-Physiologically Based Pharmacokinetic (p-PBPK) models in order to predict foetal PK profiles.

With our models we simulated foetal PK profiles for 3 antiretroviral drugs, tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) and lamivudine (3TC). We compared these predictions to observed cord blood plasma concentrations to support the validity of our models.



VE: Venous blood, AR: Arterial blood, LU: Lung, AD: Adipose, BO: Bones, BR: Brain, HE: Heart, MU: Muscle, SK: skin, PA: Pancreas, SP: Spleen, GU: Gut, LI: liver, RB: rest of the body, Amn Fluid: Amniotic fluid, QplM: blood flow from the mother to the placental tissue, QplF: blood flow from the foetus to the placental tissue, QrbF: blood flow to the foetal body, D_{pl}: diffusion, k_{sw}: swallowing constant, CL_{rF}: foetal urinary excretion, k_{PE}: placental elimination

RESULTS

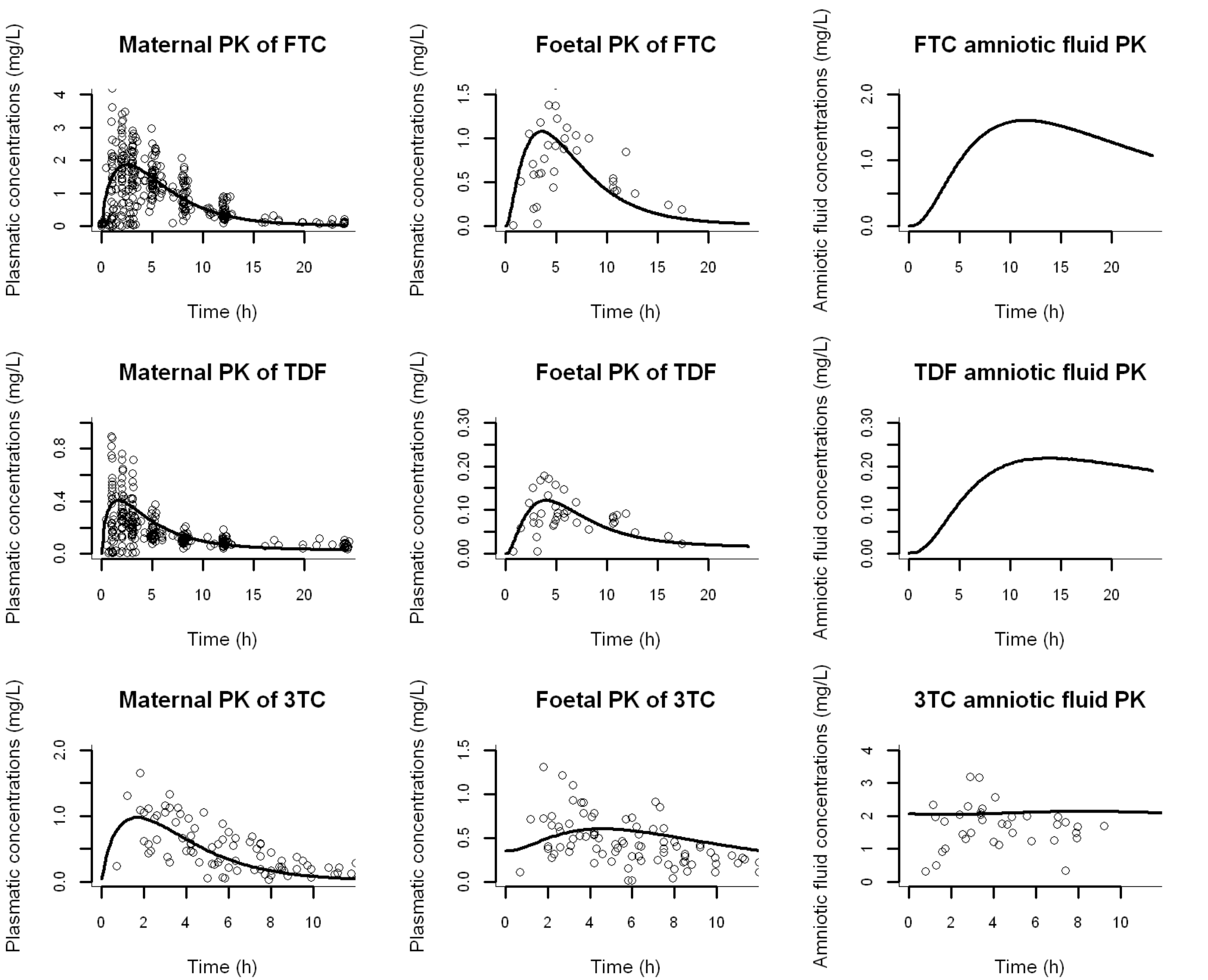
EX VIVO EXPÉRIMENTATIONS

The mean (±SD) antipyrine foetal transfer rate was 53.9% (±5.9 %) for tenofovir and 42.9 % (± 3.7 %) for FTC.

	D _{cot} (L/h)	k _{PE} (h ⁻¹)	k _{ppl}
Emtricitabine	0.104	1.49	3.94
Lamivudine	0.055	0*	1*
Tenofovir	0.0127	0.443	7.15

Diffusion model best fit observed ex-vivo data, Placental coefficient partition (k_{ppl}) and placental elimination (k_{PE}) were estimated for FTC and TDF. There were fixed (*) for 3TC.

PK PROFILE SIMULATIONS

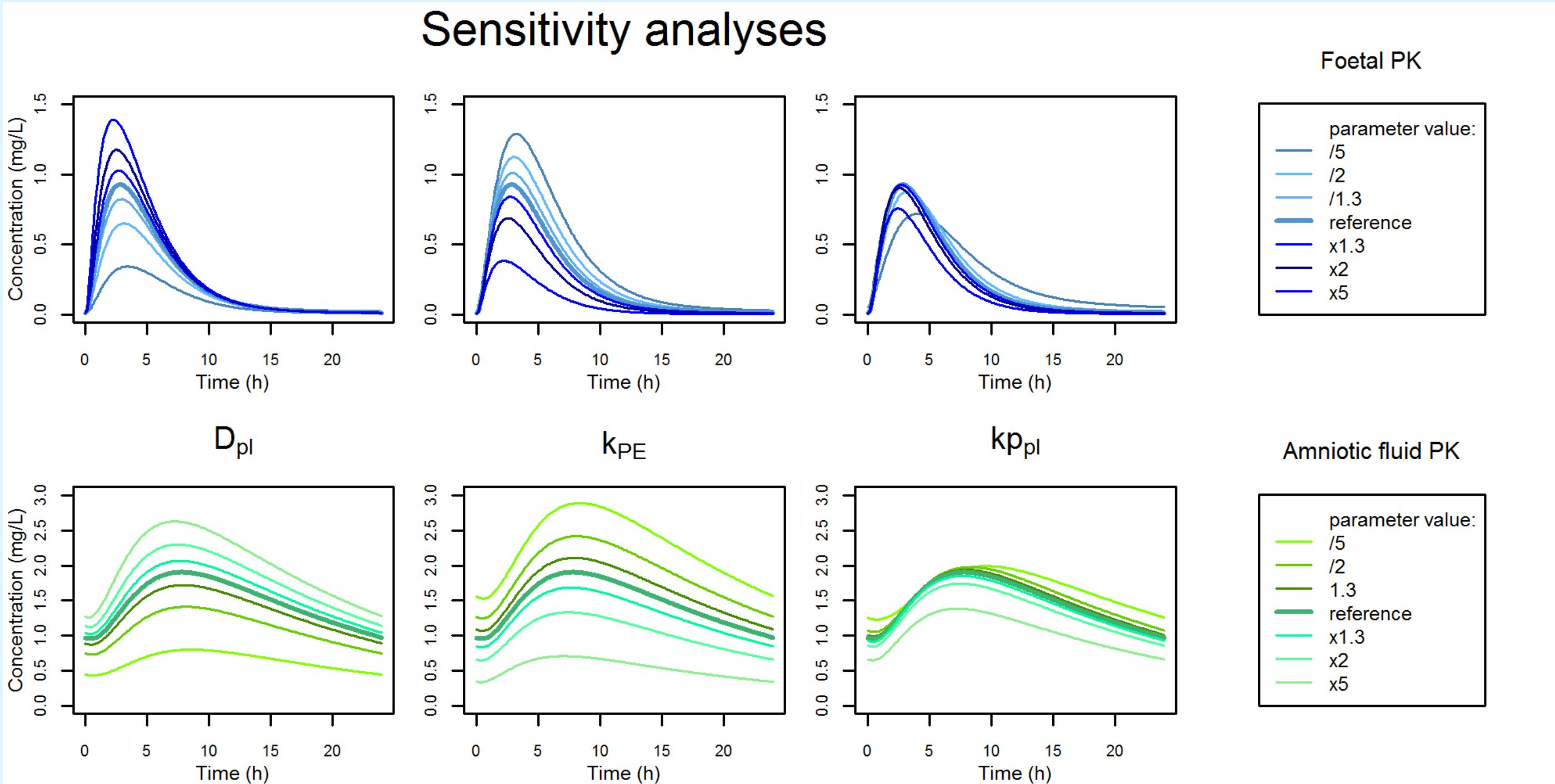


Simulated foetal PK profiles using our p-PBPK model and placental transfer obtained with the ex-vivo model closed to observed cord concentrations.

GA=39		FTC	3TC	TDF
Single dose	Plasmatic AUC _f /AUC _m	0.63	0.86	0.41
	Amniotic fluid AUC/plasmatic maternal AUC _m	1.93	2.47	1.39
steady state	Plasmatic AUC _f /AUC _m	0.64	1.18	0.45
	Amniotic fluid AUC/plasmatic maternal AUC _m	3.43	6.60	2.76

Foetus are significantly exposed to these drugs and there are an amniotic fluid accumulation. Foetal maximal concentrations are smaller than maternal ones but minimal concentrations higher.

Sensitivity analyses showed that the diffusion (D) and placental elimination (k_{PE}) parameters values were strong determinants of simulated foetal and amniotic fluid PK profiles.



CONCLUSION

Diffusion parameters and placental elimination values obtained from the ex-vivo model allowed good predictions of foetal PK profile. Moreover the sensibility analyse performed on these parameters showed that any modifications significantly impact foetal exposure. Thus, the ex-vivo model, combined with PBPK model, seems to be a sensitive and accurate method to predict foetal exposure.

The present approach allows basic prediction of foetal PK prior drug administration to the mother. This should be a useful tool for drug discovery, drugs targeting the foetus or drugs that can potentially be used at full-term pregnancy.