

A physiologically based pharmacokinetic model for a drug metabolized by several CYP450 during pregnancy

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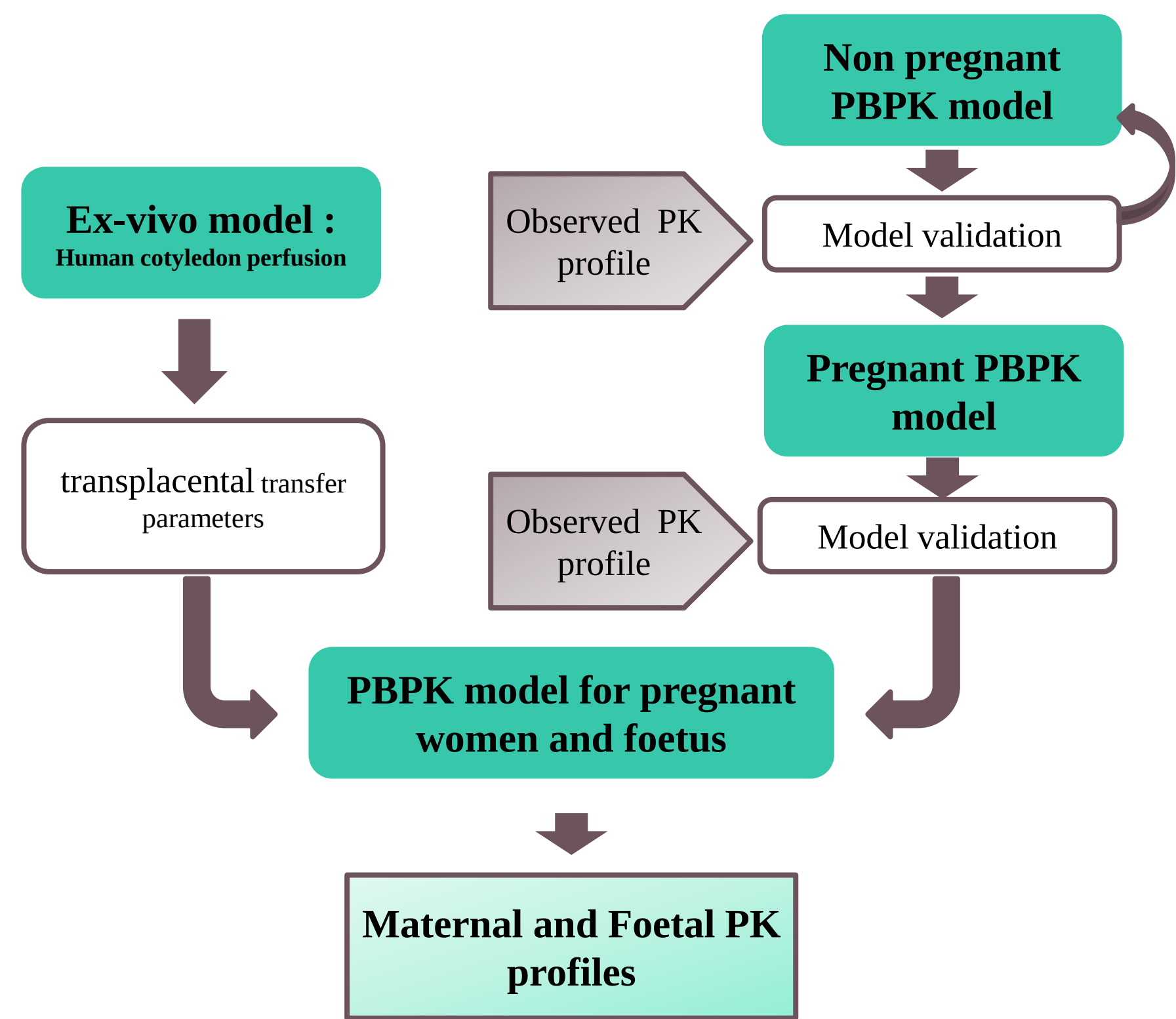
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INTRODUCTION

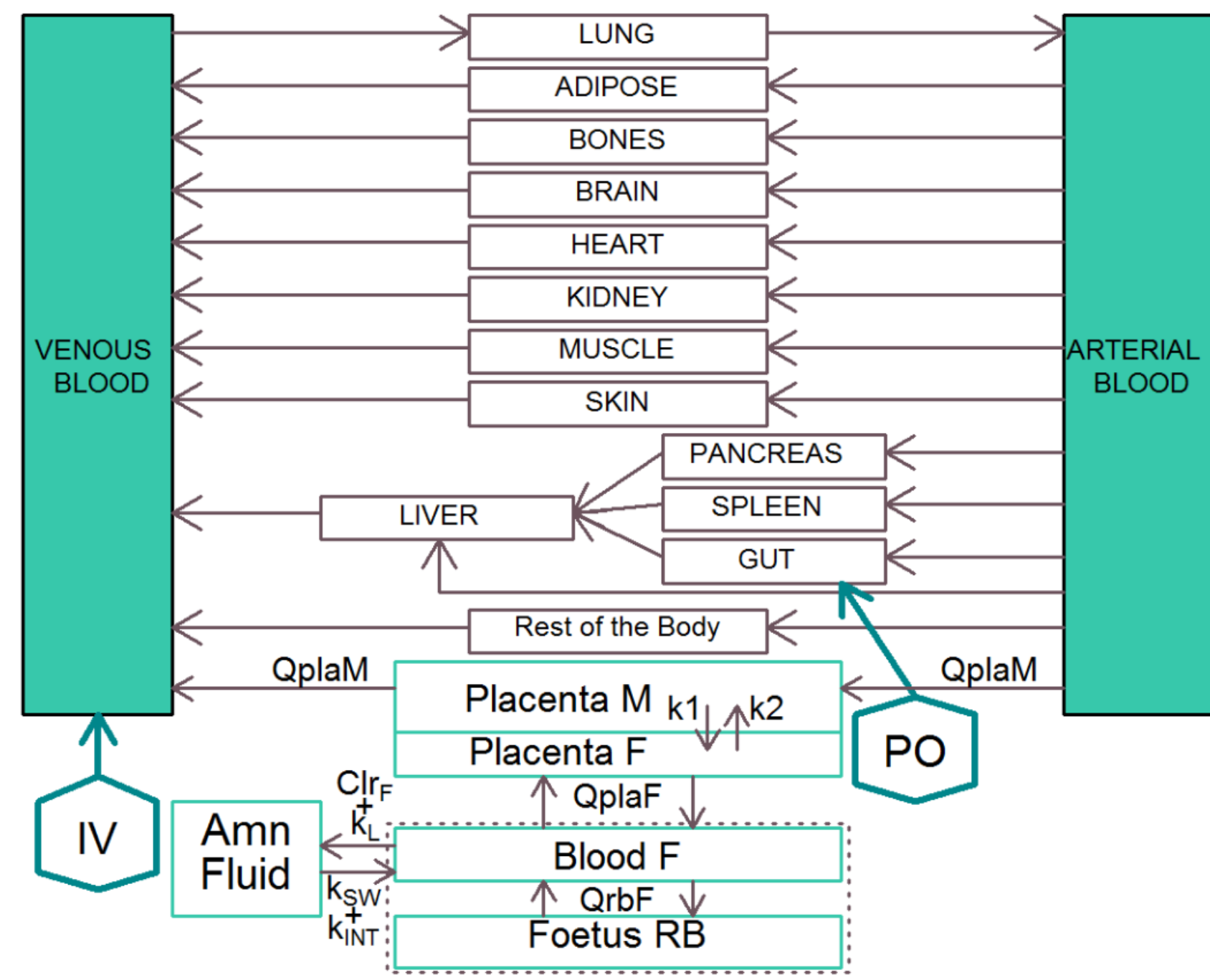
Pregnant women and foetuses are orphan populations with respect to the safety and efficacy of drugs. However they are exposed to numerous compounds. Therefore the prediction of maternal and foetal pharmacokinetics is highly desirable. Physiologically Based Pharmacokinetic (PBPK) models have already been used to predict maternal pharmacokinetics (PK). However few of them have focused on the prediction of foetal exposure.

METHODS



We firstly developed nevirapine (NVP) **PBPK model** for non-pregnant population. When the model adequately described observed concentrations after oral and intravenous administration for a single dose and at steady state we implemented all **physiological changes** occurring during pregnancy. Then we predicted and compared the pharmacokinetic profile to observed concentrations in pregnant women. **Transplacental transfer parameters** were estimated from the **human cotyledon perfusion experiment**. These parameters were implemented into the PBPK model. Thus foetal PK profile was predicted and compared to observed **cord blood plasma concentrations**.

A sensitivity analysis was performed on physiological foetal parameters and transplacental transfer parameters to evaluate their impact on foetal and amniotic fluid PK. As elimination pathways are not well known for foetuses, we evaluated if foetal metabolism could have an impact on foetal PK.



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, Qplam: blood flow from the mother to the placental tissue, Qplaf: blood flow from the foetus to the placental tissue, Qrbf: blood flow to the foetal body, k1 and k2: transplacental transfer parameters, k_{sw} : swallowing constant, $CL_{rfoetus}$: foetal urinary excretion,

RESULTS

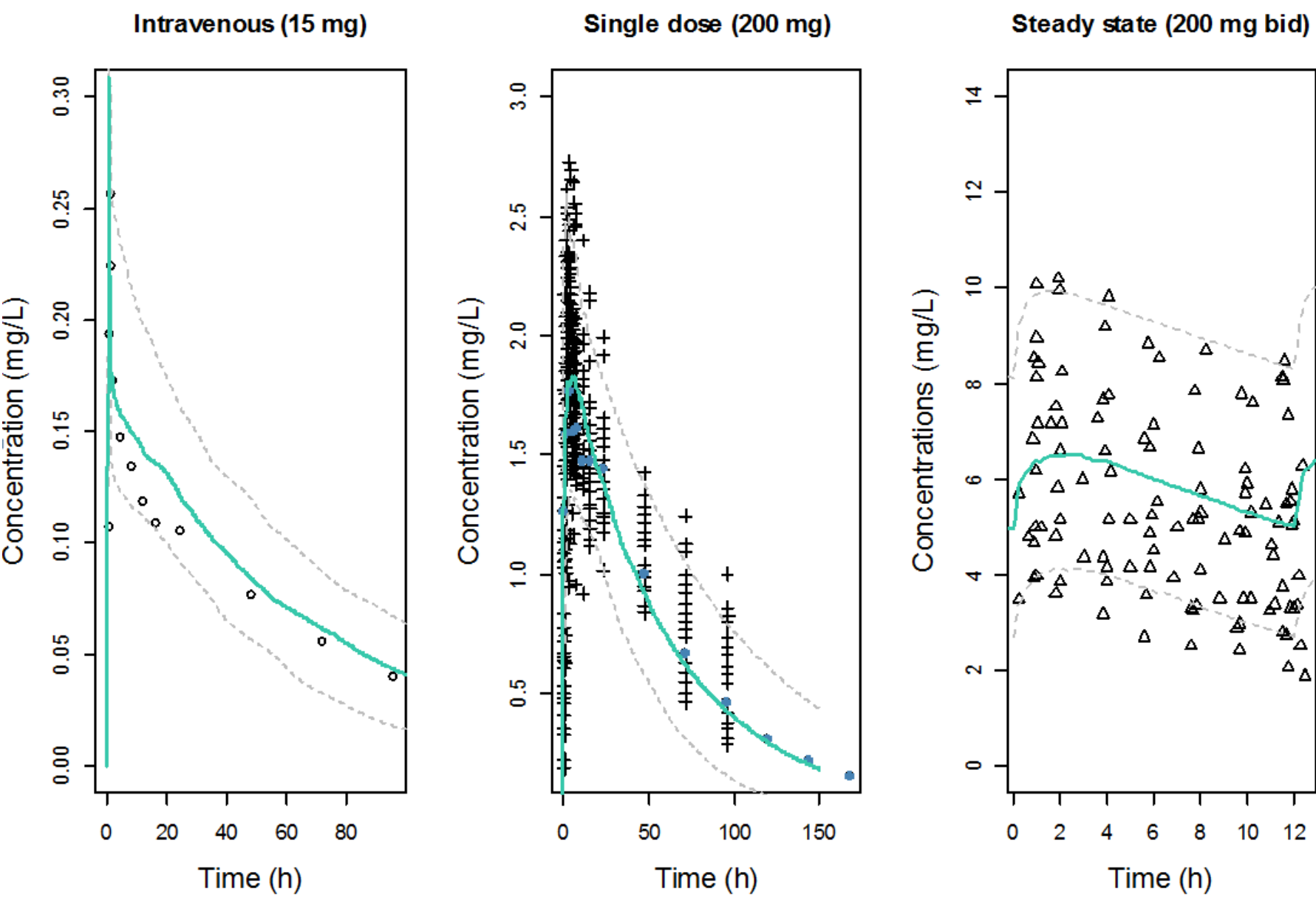
EX VIVO EXPÉRIMENTATIONS

From the *ex-vivo* experiment (human placenta), transplacental transfer parameters (k_1 and k_2) and placental coefficient partition (kp_{pl}) were estimated in MONOLIX.

Parameter	Estimate	RSE (%)
k_{1cot} (h^{-1} per cotyledon)	0.171	10
k_{2cot} (h^{-1} per cotyledon)	0.208	3
kp_{pl} (unitless)	3.7	15
ηk_{1cot}	0.338	23
ηkp_{pl}	0.513	24
$\sigma_{prop} C_m$	0.113	7
$\sigma_{cst} C_f$	0.079	8

NON PREGNANT POPULATION

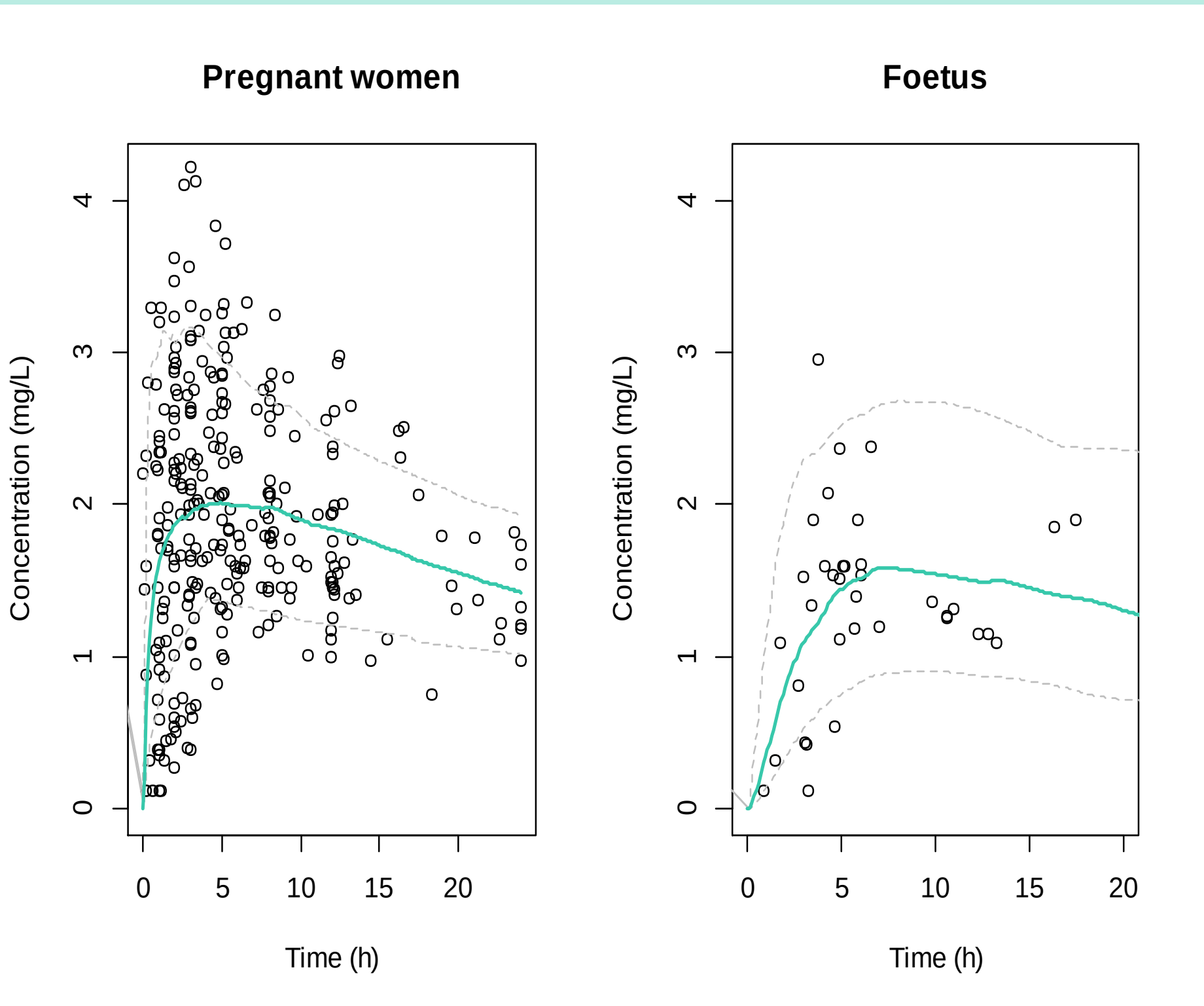
Our model was able to correctly describe NVP pharmacokinetics following 15 mg intravenous administration, single 200 mg oral dose and for multiple 200 mg oral doses.



PREGNANT POPULATION

Because of **CYP3A4, 2D6 and 2B6 inductions**, we predicted a clearance **increase of 21 % and 38 %** in late pregnancy after a single dose administration and at steady state respectively.

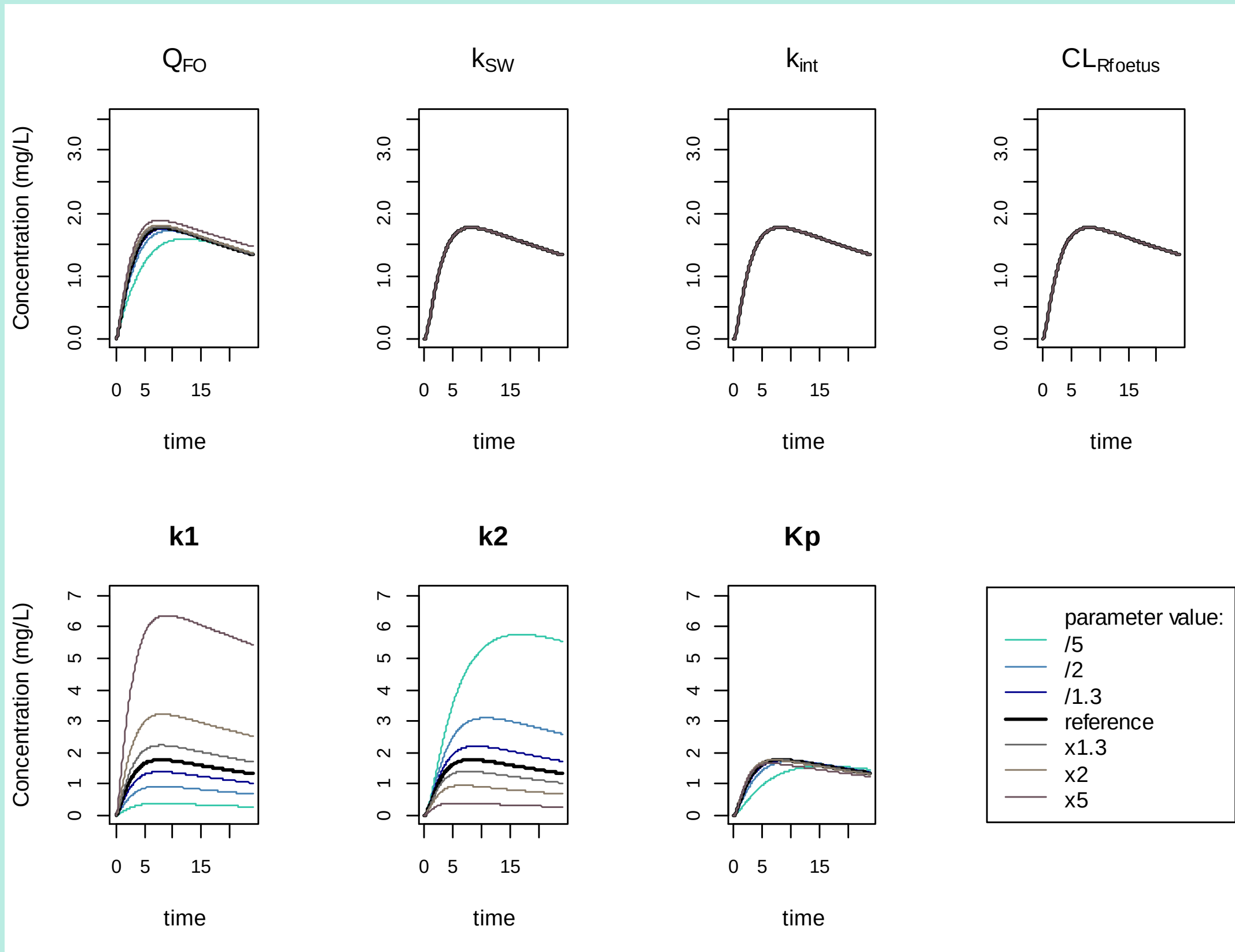
Simulated foetal PK profiles using our PBPK model were in agreement with observed cord blood concentrations. At delivery **foetal-to-maternal AUC_{24}^0 ratio has been predicted to be 77 %** for a single dose of NVP. The predicted AUC_{∞}^0 ratio for a single dose was 84 %.



Sensitivity analyses were done on **foetal physiological parameters**. The figure shows that foetal renal excretion ($CL_{Rfoetus}$), intramembranous pathway and swallowing constant had **no significant impact** on foetal PK profile. The **transplacental transfer parameters** estimated from the human cotyledon experiments have been shown to be **key parameters** to predict the foetal PK profile: if k_1 value was divided by two, the foetal maximal concentrations were also approximately divided by two.

Implementation of **foetal metabolism** based on newborn clearance **did not change foetal AUC**. Even if this elimination was multiplied by 2, no change in foetal AUC or PK profile could be seen.

Sensitivity analyses



CONCLUSION

Placental parameters 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.