

VALIDATION OF A POPULATION PBPK MODEL FOR PREGNANT WOMEN



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Objectives

The goal of this study is to evaluate a physiologically-based pharmacokinetic (PBPK) model for the prediction of pharmacokinetics (PK) of small molecule drugs in populations of pregnant women at different stages of gestation.

Introduction

Pregnant women represent a special population with respect to drug therapy. As they are generally excluded from clinical trials, there is scant information on the PK. PBPK modeling is considered as a promising approach to predict the PK in pregnancy. Although first attempts to build pregnancy PBPK models have been made, a fully mechanistic population PBPK model is still under evaluation. To address this issue, we set out to verify a newly developed population PBPK model for pregnant women.

Methods

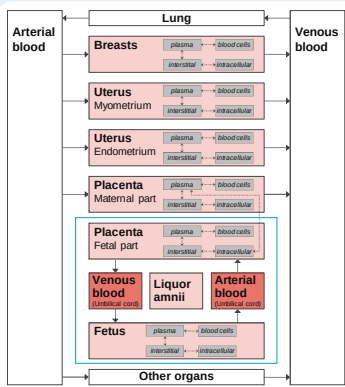


Fig. 1: Structure of the pregnancy PBPK model. The pregnancy PBPK model was developed based on the standard model structure for an adult female [2]. This structure was extended by 9 physiological compartments that are either specific to pregnancy (e.g. placenta and fetus) or become of specific relevance during pregnancy (uterus and breasts). The new compartments are drawn in light red and dark red in case of blood pools. The compartment termed "Other organs" includes all compartments of the standard structure that are not explicitly shown in this figure. Solid arrows represent drug transport pathways via blood flow and dotted arrows via passive diffusion. The blue frame encloses the fetal organism.

Based on a recent literature review on anatomical and physiological changes during pregnancy [1], a pregnancy population PBPK model has been developed (Fig. 1) using the software PK-Sim®/MoBi® [2]. Populations of pregnant women were created using the organ scaling approach implemented in PK-Sim® [3].

The pregnancy population PBPK model was applied to predict the PK of drugs that are either cleared renally or hepatically via CYP 1A2 (Tab. 1). The fetal contribution to total clearance was considered to be negligible due to the small size of the fetus and the absence of CYP 1A2 in fetal tissues. For model verification, predicted PK profiles were compared with experimentally observed *in vivo* data taken from the literature [4,5].

Tab. 1: Drugs used for model evaluation

Drug name	Administration	Major route of elimination	Gestational week of study participants (median [range])
Cefazolin (CFZ)	IV infusion	Renal (filtration & secretion)	24 [19 – 33]
Cefradine (CFD)	peroral	Renal (filtration & secretion)	20 [13 – 33]
Caffeine (CAF)	peroral	Hepatic (CYP 1A2)	37 [30 – 40]

Results I: Population PK predictions

The pregnancy population PBPK model successfully predicted the PK of CFZ, CFD and CAF. The predicted plasma concentrations showed good agreement with the observed *in vivo* data (Fig. 2 and 3).

We observed an underestimation of the predicted variability in early time points, especially after IV administration. The main reason for this might be that parameters relevant for distribution, e.g. fraction unbound and partition coefficients, are not varied in the virtual populations, which is a general challenge in PBPK modeling.

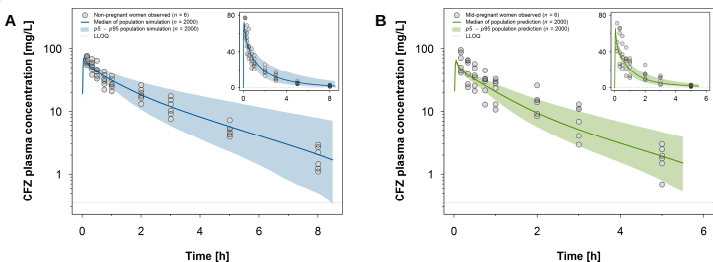


Fig. 2: Population PK profiles of cefazolin (CFZ). PK profile of CFZ in a population of non-pregnant women (A) and in a population of pregnant women with a median gestational age of 24 weeks (B). Linear scale figure in top right corner. Observed data from [4].

Results II: Population PK predictions & model diagnostics

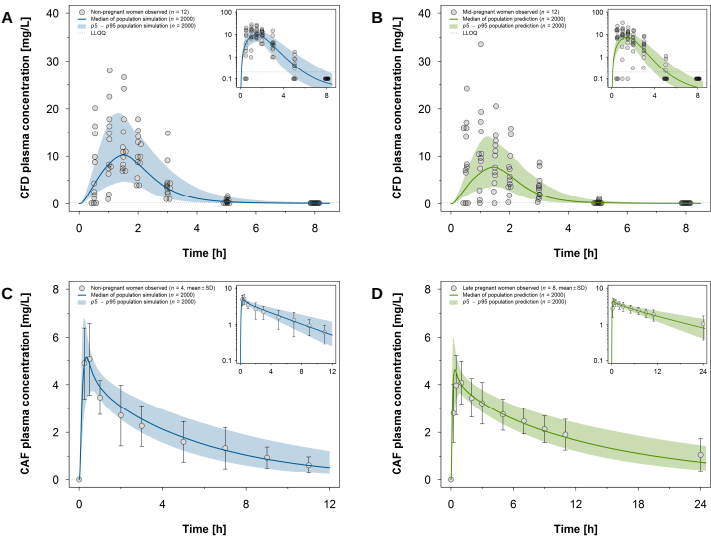


Fig. 3: Population PK profiles of cefradine (CFD) and caffeine (CAF). Upper panel: PK profile of CFD in a population of non-pregnant women (A) and in a population of pregnant women with a median gestational age of 20 weeks (B). Semi-log scale figure in top right corner. Data values below LLOQ were included as half LLOQ. Observed data from [4]. Lower panel: PK profile of CAF in a population of non-pregnant women (C) and in a population of pregnant women with a median gestational age of 37 weeks (D). Semi-log scale figure in top right corner. Observed data from [5].

The simulated and predicted concentrations fell within a 0.5- and 1.5-fold error range in case of CFZ and CFD, respectively. Simulated and predicted CAF concentrations were all within a 0.75-fold error range (Fig. 4A).

For CFZ and CFD, no changes in the activity of renal transporters involved in clearance were necessary to correctly predict the observed *in vivo* PK. This indicates that the activity of the renal transporters OAT 1, OAT 3, MATE 1, and MRP 4 remains essentially constant throughout pregnancy.

Our population PBPK model captured the twofold increase in CAF exposure in late pregnancy compared to non-pregnant women. In our model, this increase is primarily explained by a 60% decrease in CYP 1A2 activity towards term.

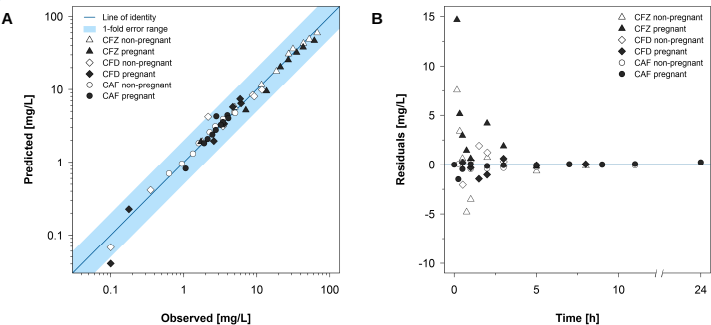


Fig. 4: Diagnostics of model performances. Goodness-of-fit plot (A) and residuals-vs-time plot (B) for the simulated and predicted CFZ, CFD and CAF plasma concentrations in pregnant and non-pregnant women, respectively. The observed CFZ and CFD concentration data were combined at each time point to geometric mean values.

Conclusions

We successfully developed and verified our pregnancy population PBPK model at different stages of gestation for drugs that are predominantly cleared via the kidneys or hepatically via CYP 1A2. PK changes in pregnant women could be mainly attributed to pregnancy-related changes in relevant parameters such as renal volume and blood flow or CYP 1A2 activity. Ultimately, this model can be applied to investigate *in silico* the PK of relevant drugs and help design clinical trials in this vulnerable population.

References

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