Extension Of A Pregnancy PBPK Model For Renally Cleared Drugs To The Postpartum Period

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Objectives

The objective of this study is to extend a physiologically-based pharmacokinetic (PBPK) model for pregnant women to the postpartum period and to verify it for the prediction of amoxicillin pharmacokinetics (PK) in the early postpartum period.

Introduction

The efforts to understand how physiological changes in pregnancy affect the drug PK have considerably increased over the past years. As a result, the literature now abounds with clinically relevant PK changes in pregnant women. Yet, these efforts surprisingly wane with respect to the period following delivery, even though the physiological changes induced by pregnancy do not promptly return to the pre-pregnant state. Drug use, at the same time, is frequent in postpartum women [1,2].

The altered physiology may be maintained for a while or even further exaggerated before pre-pregnant levels are eventually restored. Hence, dose adjustments may be indicated in postpartum women to obtain an optimal therapeutic outcome. PBPK modeling can be a useful tool to investigate PK changes *in silico* when extensive *in vivo* PK trials are not feasible, as is the case for postpartum women. Therefore, this study aims at developing a PBPK model for the postpartum period.

Methods

A systematic literature search was carried out to collect study data on anatomical and physiological changes in the postpartum period. Collected data were quality appraised and compiled in a database if they met the predefined inclusion criteria shown in Tab. 1. Using a previously described approach [3], mathematical functions were fitted to the data to quantitatively describe the anatomical and physiological dynamics observed in the postpartum period.

Tab. 1: Inclusion criteria of the studies collected from the literature

Inclusion criteria	
Singleton, healthy pregnancy preceeding the postpartum period	☑
Predominantly Caucasian ethnicity	☑
No medication known to interfere with physiological parameters	☑
Accurately reported postnatal age	☑

The generated functions were combined with previously reported functions for pregnancy-dependant changes [3,4] and implemented in PK-Sim® and MoBi® as part of the Open Systems Pharmacology Suite (www.open-systems-pharmacology.org). Finally, a postpartum PBPK model was developed and used for predicting the disposition of amoxicillin, a primarily renally cleared drug, admnistered 1.5 – 3.8 hours after delivery. PK predictions were verified using *in vivo* data from the literature [5,6].

Results I: Literature review

Fig. 1: Absolute frequency of data collected from the literature. 46% of the data were reported within the first 8 weeks and 68% within the first 16 weeks after delivery.

The literature search yielded 105 studies with 1092 anatomical and physiological data values (including mean values) obtained from 3742 postpartum women. These data encompassed a period from 1 h – 130 weeks after delivery (Fig. 1). With a few exceptions, e.g. volume and blood flow of the breast tissue, all parameters appeared to have returned to pre-pregnant levels at the latest by the 16th week after delivery.

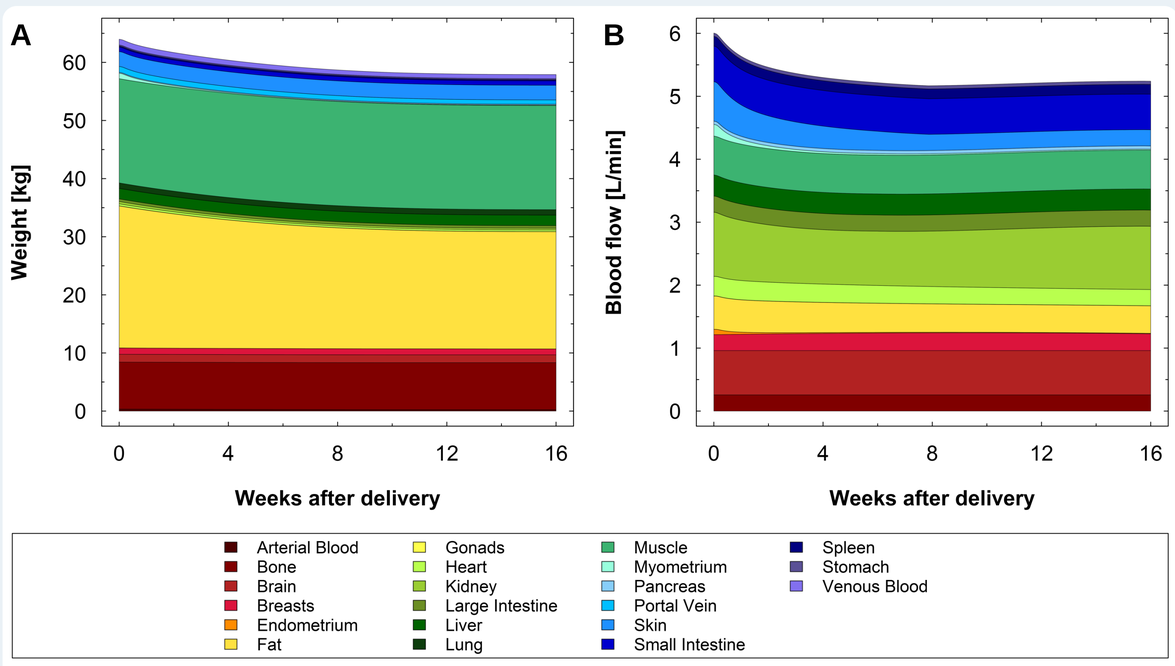

Fig. 2: Body composition and organ blood flows in the postpartum period.
Changes are shown up to the 16th week after delivery where most parameters have returned to the pre-pregnant level. (**A**) Mean body composition of a typical postpartum women. (**B**) Mean organ blood flows of a typical postpartum women.

Results II: PBPK model for amoxicillin

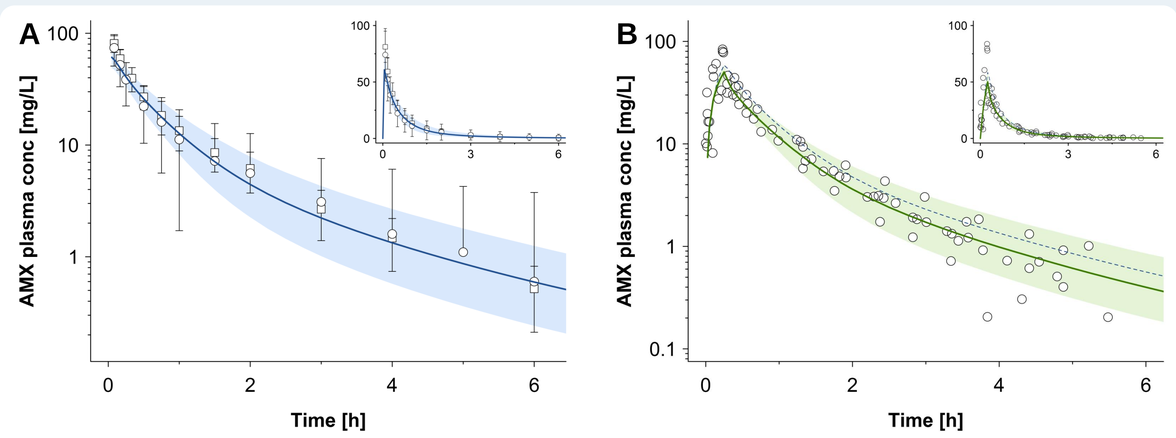

Fig. 3: Disposition profiles of amoxicillin in populations of normal subjects (left panel) and postpartum women 1.5 – 3.8 hours after delivery (right panel).
Solid lines represent the simulated or predicted mean plasma concentration; the shaded area the simulated or predicted 5th – 95th percentile range; and symbols the observed *in vivo* data. Linear scale figure in top right corner. (**A**) Amoxicillin PK profile in non-pregnant subjects after IV bolus administration of 1000 mg; observed *in vivo* data (mean ± SD) after administration of 500 mg (circles) and 1000 mg (squares) taken from [5,6]; concentrations dose-normalized to 1000 mg. (**B**) Amoxicillin PK profile in postpartum women 1.5 – 3.8 hours after delivery after IV administration of 1000 mg over 15 min. Observed data are (individual values) taken from [7]. For comparison purposes, the dotted line shows the predicted plasma concentration in a virtual population of normal women with the same body weight than postpartum women receiving the same amoxicillin dose.

The postpartum PBPK model successfully predicted the disposition of amoxicillin 1.5 – 3.8 hours after delivery. The mean plasma concentrations simluated in normal subjects and those predicted in postpartum women were in good agreement with the observed *in vivo* data (Fig. 3). In normal subjects, all simulated concentrations fell within a 2-fold error range, while in postpartum women 91% of the predicted concentrations lay within that range (Fig. 4).

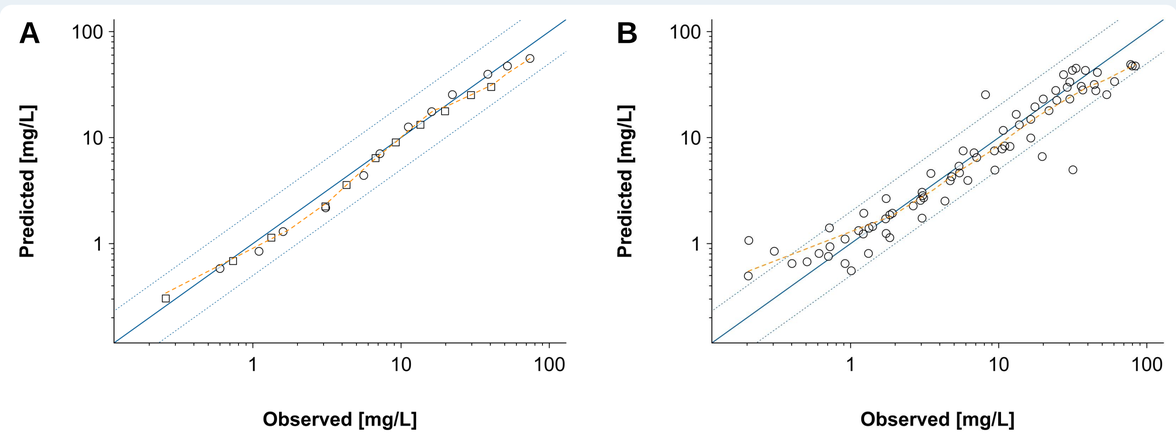

Fig. 4: Goodness-of-fit plot for amoxicillin disposition in populations of normal subjects (A) and populations of postpartum women 1.5 – 3.8 hours after delivery (B).
The solid line represents the line of identity; dotted lines the 2-fold error range; and the dashed line a local regression (LOESS) curve. Observed data in (A) are mean values and taken from [5] (administration of 1000 mg; circles) and [6] (administration of 500 mg; squares); observed data in (B) are individual values and taken from [7].

Amoxicillin exposure was adequately predicted by the PBPK models. In normal subjects, the ratio of simulated to observed mean AUC_{inf} was 1.03 (simulated: 44.3 mg h/L; observed: 43.0 mg h/L [6]). In contrast, in postpartum women the ratio of predictedto observed mean AUC_{inf} was 0.98 (predicted: 39.1 mg h/L; observed: 38.4 mg h/L [7]).

Moreover, no changes in specific tubular secretion were necessary to correctly predict the observed *in vivo* data in postpartum women. This indicates that the activity of the renal transporter involved in amoxicillin excretion, the organic anion transporter, remains unchanged in early postpartum women.

Conclusions

A set of mathematical functions describing anatomical and physiological changes during the postpartum period was developed and coupled to a previously presented pregnancy PBPK model [4]. Subsequently, a postpartum PBPK model was developed and successfully applied to predict the *in vivo* disposition of amoxicillin a few hours after delivery. To increase the confidence in the presented postpartum PBPK model, further PK predictions should be carried out, especially for drugs administered at later time points in the postpartum period. Ultimately, such a model could be applied to investigate the PK of drugs in the postpartum period including potential drug transfer to the neonate via breast-feeding *in silico*.

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