DEVELOPMENT OF A PHYSIOLOGICALLY-BASED PHARMACOKINETIC POPULATION MODEL FOR PREGNANT WOMEN

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Objectives
The goal of this study is to develop a physiologically-based pharmacokinetic (PBPK) model for the prediction of the pharmacokinetics (PK) of small molecule drugs in healthy Caucasian pregnant women from conception to term.

Introduction
Pregnant women represent a special population with respect to drug therapy. Drug use in pregnant women is frequent and increasing [1]. Yet, information on dosing is widely lacking because pregnant women are usually excluded from clinical trials. Consequently, mother and fetus are at high risk of incorrect pharmacotherapy with suboptimal or toxic drug effects in mother or even fetus. Better understanding of the PK in pregnant women is urgently needed to optimize dosing regimens.

Since extensive in vivo PK studies in pregnant women are neither desirable nor feasible, PBPK modeling is considered as a promising approach for predicting the PK of drugs in pregnant women. Although first attempts to build PBPK models for pregnant women have been made, the FDA concluded recently that the experience with those models is still limited [2]. Further research is therefore needed to draw sound conclusions on the predictive performance of PBPK models in this special population.

Methods

I: Literature review

<table>
<thead>
<tr>
<th>Preliminary study set</th>
<th>Final study set</th>
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</thead>
<tbody>
<tr>
<td>Studies available in literature</td>
<td>Data extraction</td>
</tr>
<tr>
<td>PK data of each study</td>
<td>Curve fitting</td>
</tr>
<tr>
<td>(j) mean model</td>
<td>(j) variability model</td>
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<td>Selection of best model</td>
<td>Figure 1: Workflow of this study: First, a literature review was carried out to collect studies on relevant changes during pregnancy. Studies were included if they met the inclusion criteria and had no technical flaws. In a second step, the data were entered and a set of mathematical functions was fitted to the data and to their variability. The best models were chosen, yielding an average model (j) for the mean and a variability model (j) describing the standard deviation for each parameter as a function of gestational age.</td>
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A systematic literature search was carried out to identify and collect study data on pregnancy-related changes of anatomical, physiological, and functional parameters to establish a PBPK population model for pregnant woman. Each study was quality appraised and the data were extracted if the study met the inclusion criteria (Tab. 1).

The extracted data were analyzed and compiled in a database. A set of mathematical functions was fitted to the data and the best performing function selection was based on numerical and visual diagnostics together with literature support. As value for the numerical diagnostics the corrected Akaike information criterion was applied [3].

Table 1: Inclusion criteria of the studies collected from the literature

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<tr>
<th>Inclusion criteria</th>
<th>Number of studies</th>
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<td>Singleton pregnancy of healthy adult women</td>
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<td>Predominantly Caucasian ethnicity</td>
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<tr>
<td>No medication during pregnancy</td>
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<td>Accurately reported gestational age (GA)</td>
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The mathematical functions were implemented in PK-Sim®/MoBi® [4]. Parameters for which minimal or no data could be found, such as brain or bone volume, were set to the values of non-pregnant women and were kept constant throughout gestation.

Results I: Literature review

The literature search yielded 279 final studies with 9409 anatomical, physiological, and functional data on 430,507 healthy pregnant women. These data comprised information on 28 out of 50 parameters. Importantly, rich data were found for many relevant parameters such as cardiac output, uterine blood flow and placental volume.

Results II: Data analysis

Figure 3: Plasma volume changes during pregnancy: (A) Literature data on plasma volume. Blue line: (j) describing the mean plasma volume against GA. (B) Literature data on the standard deviation of the plasma volume. Blue line: (j) describing the standard deviation of the plasma volume against GA. (C) Literature data on plasma volume error bars indicate the standard deviation. Solid blue line: (j). Dashed blue line: (j) ± (j).

For all 28 parameters with available data from the literature, mathematical functions were generated describing changes in the mean and variability of the parameter during pregnancy. They were implemented in a prototype whole-body PBPK population model for healthy Caucasian pregnant women.

The sum of the mean weights of all included organs and tissues amounts to 92 – 94% of the total gestation-specific body weight. The difference is caused by some organs and tissues that were not accounted for in the model, e.g. ureters, urinary bladder, and thyroid. The weight gain of all included organs and tissues throughout pregnancy is, on average, 12.0 kg which is consistent with literature data [5]. The sum of the weights of all included organs and tissues in the 84th percentile adds up to 98 – 101% of the total gestation-specific body weight.

Figure 4: Body composition during pregnancy: (A) Mean body composition of typical pregnant women. (B) Body composition of pregnant women in the 84th percentile which was estimated for each organ as (j) + 1.96(j). For comparison, the corresponding body composition of nonpregnant women is shown in graded colors until the beginning of the 2nd gestational week where, on average, conception occurs.

Conclusions
A set of mathematical functions describing changes in anatomical, physiological, and functional parameters throughout the course of pregnancy is developed and implemented in a longitudinal and time-varying prototype whole-body PBPK model for healthy Caucasian pregnant woman. Ultimately, this model could be applied to investigate the PK of drugs in silico in this vulnerable population.

References