A Time-varying Physiologically-Based Pharmacokinetic Model of Caffeine during Pregnancy

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Objectives

To develop a time-varying physiologically-based pharmacokinetic (PBPK) model to consider anatomical and physiological changes during pregnancy.

The Pregnancy PBPK Model

The *pregnancy PBPK model* is based on a similar structure of Simcyp full-PBPK model, which consists of 13 compartments representing various tissues, namely, adipose, bone, brain, heart, lung, kidney, gut, muscle, spleen, skin, liver, arterial and venous blood. A *pregnancy tissue compartment*, which represents overall fetus, uterus, placenta, amniotic fluid, and mammalian glands, is added in parallel to other tissue compartments (Figure 1).

Anatomical and physiological changes during pregnancy were modelled using *gestational time-dependent parameters* and included in the respective compartments. Examples of these parameters are tissue volume and composition, cardiac output and blood flow. An extensive and structured literature search was carried out to identify the raw data for the pregnancy modelling. This included information on a normal singleton pregnancy, mainly from Caucasian women (reference list is available upon request). Basal values for various parameters in a non-pregnant woman were set as defined in Simcyp V.10 (Ahamadi et al., 2010).

The *governing equations* in the pregnancy PBPK model describing time-dependent caffeine concentration are based on mass conservation law and have been implemented in Simulink®.

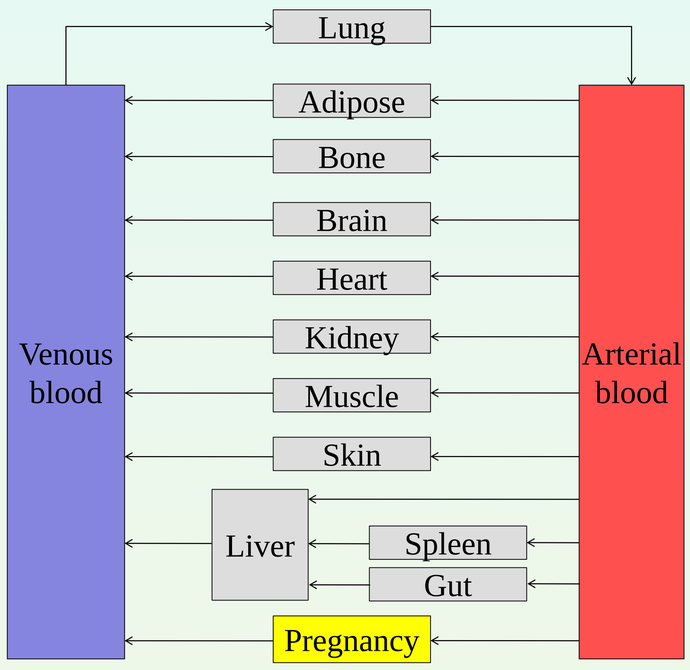

Figure 1. Structure of pregnancy PBPK model.

Simulation results

- Plasma concentration

Simulation results of plasma concentration, for both pregnant and non-pregnant women, were in line with a previously reported study (Brazier et al., 1983). Administration of an oral dose of 150 mg caffeine was simulated for pregnant (36 weeks of gestation) and non-pregnant women (Figure 2). A significant prolongation of caffeine elimination was observed in late pregnancy in comparison with non-pregnant women. The predicted plasma AUC in pregnant women (56.3 mg/L*hr) is 2-fold greater than that in non-pregnant women (27.2 mg/L*hr).

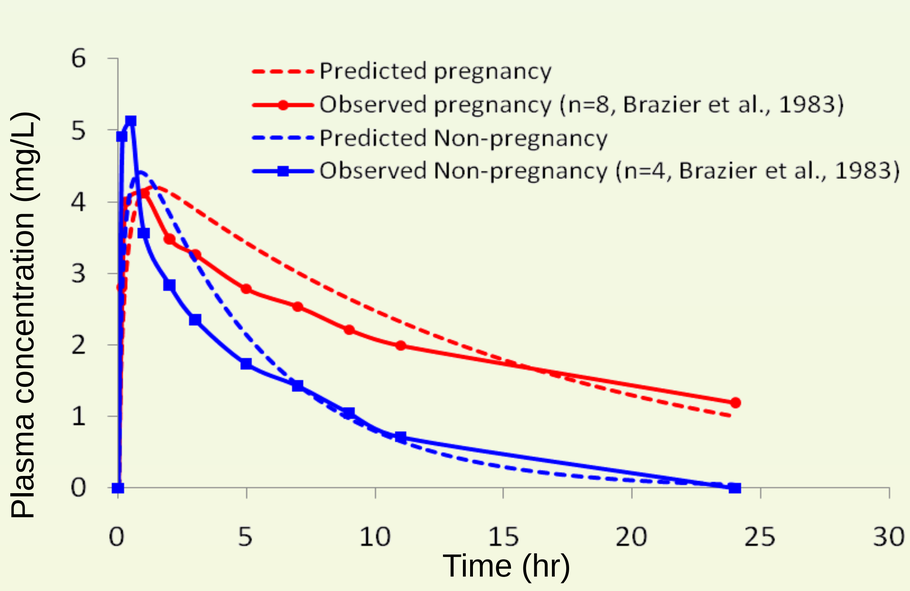

Figure 2. Predicted and observed plasma caffeine concentration.

- Impact of gestation period

The model shows that the areas under time-concentration curves (AUC) for caffeine in plasma and in pregnancy tissue increase with the progression of gestation (Figure 3). The rate of increase in the pregnancy tissue AUC is larger in the first trimester, compared to that in the second and/or third trimester. Both the plasma AUC and the pregnancy tissue AUC decrease slightly in the last several weeks before delivery.

The simulation results are consistent with the clinical observation of prolongation of caffeine elimination, which is mainly affected by reduction of CYP1A2 abundance.

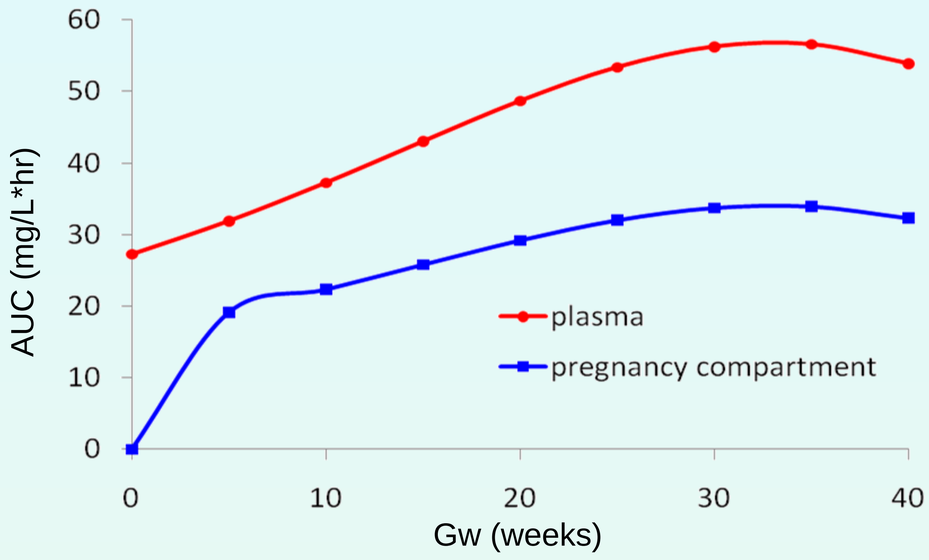

Figure 3. Impact of gestational time (Gw) on caffeine exposure.

- Impact of pregnancy tissue-plasma partition coefficient ($K_{preg:p}$)

If $K_{preg:p}$ is changed from 0.1 to 1.0, the maximum concentration (C_{max}) of caffeine in the pregnancy tissue increased by 10-fold, from about 0.4mg/L to 3.7mg/L, while the maximum plasma concentration decreased from 4.3mg/L to 3.7mg/L (Figure 4).

Monitoring plasma concentration of caffeine may not be sufficient to capture changes in pregnancy tissue concentration as $K_{preg:p}$ may vary significantly during pregnancy. However, accurate knowledge of this concentration is essential to clinicians. Information on $K_{preg:p}$ from clinical practice is desirable to improve model performance.

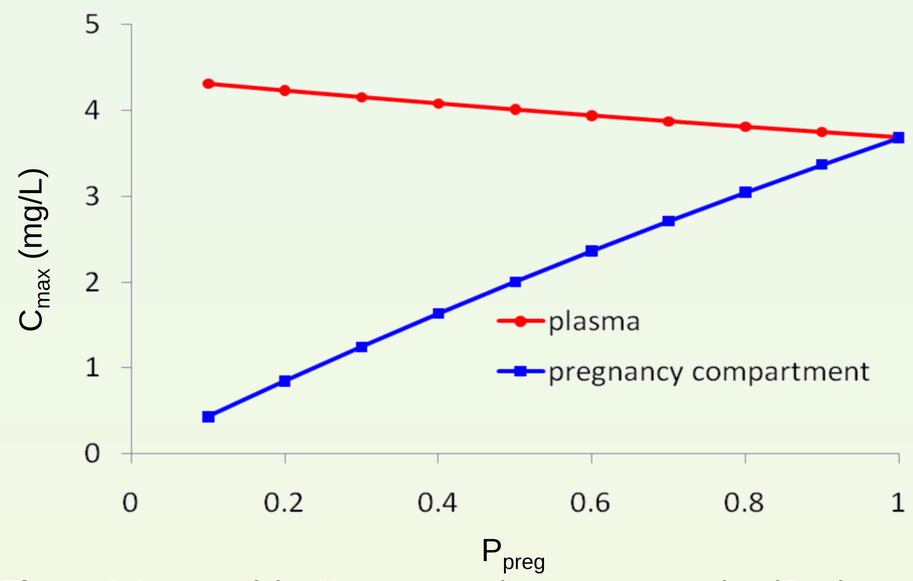

Figure 4. Impact of the $K_{preg:p}$ on maximum concentration (C_{max}) in plasma and in pregnancy tissue.

Conclusions

A PBPK model, whose system parameters change during pregnancy, has been developed and implemented in Simulink.

The pregnancy PBPK model has successfully simulated caffeine disposition in pregnant women.

The model will be validated further for more drugs.

References

(1) Ahamadi *et al.*, *A guide for IVIVE and PBPK Modelling using the Simcyp population-based ADME simulator, Version 10*. Sheffield, Simcyp, 2010.

(2) Brazier *et al.*, Pharmacokinetics of caffeine during and after pregnancy. *Dev Pharmacol Ther* 1983;6(5):315-322.