A Pregnancy Physiologically Based Pharmacokinetic Model Verified For Different Drugs Metabolized And Eliminated Via Various Pathways

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Objectives: To establish a physiologically based pharmacokinetic (PBPK) system parameter model basis describing anatomical and physiological changes during pregnancy and evaluate it with different test drugs eliminated via filtration, transport, or metabolism.

Methods: The system parameter model basis was consolidated from literature including information on general physiology [1] as well as on specific elimination [2] and metabolic pathways and implemented in the Open Systems Pharmacology Suite (PK-Sim®/MoBi®, [3], www.open-systems-pharmacology.org). Substance models were developed based on physico-chemical and clinical pharmacokinetic literature data for non-pregnant woman and predictions for pregnant populations were evaluated against pharmacokinetic literature data collected during pregnancy.

Results: The system specific parameters of the pregnancy PBPK model included consolidated information on pregnancy-induced parameter changes derived from 7729 data points that were reported in 302 studies. Substance PBPK models were built for 12 different drugs administered at 15 different stages of gestation. These drugs encompassed compounds eliminated via glomerular filtration, tubular secretion involving the transporters OAT 1-3, and/or metabolism via CYP 1A1/2, 2A6, 2B6, 2C19, 2D6, 2E1, and/or 3A4/5. Throughout pregnancy, drug exposure was adequately predicted by the PBPK models (Fig. 1). For all drugs, the ratio of predicted to observed AUC fell within a 1.25-fold error range.

Conclusions: A pregnancy population PBPK model was successfully developed and verified for several drugs metabolized or eliminated via various pathways. This includes examples investigated in other PBPK platforms with comparable results. These results, together with the novel examples provided here, indicate that the PBPK methodology is at least semi-quantitatively predictive and can be used to extrapolate pharmacokinetics in pregnant women. This could, for example, support the design and conduction of clinical research in this vulnerable special population.