

# Pregnancy PBPK Modeling of UGT Substrate Labetalol: An Application of Parameter Contribution Analysis to Guide Predictive Performance of Life-Stage Models



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## Abstract

Certain diseases during pregnancy require a risk versus benefit assessment of medication use to reduce harm to mother and fetus. One such example is labetalol. Since many physiological changes occur in pregnancy which can affect pharmacokinetics (PK), alternative or adaptive dosing regimens might be necessary to ensure safety and efficacy. Data scarcity from clinical trial exclusion due to ethical concerns complicates PK assessments in pregnant women. Physiologically based pharmacokinetic (PBPK) modeling is a series of mathematical equations that can help predict drug PK for dynamically changing life-stages, like pregnancy. Labetalol is metabolized by UGT2B7 and UGT1A1 which are not extensively characterized in pregnancy. Thus, in this work we quantify trimester specific parameter contributions that are most influential in describing pregnancy PK and evaluate model uncertainties in this data sparse life-stage using PBPK modeling. Based on the model we also estimate the potential contribution of UGT2B7 activity change given the uncaptured change in AUC and our confidence in the known parameters. This could help prioritize parameterization of future PBPK models and build model confidence in data-sparse life-stages, thus improving prediction capabilities and sensitivity assessments of PBPK modeling for use as a regulatory tool.

## Introduction

### Background

- Labetalol is a commonly prescribed medication in pregnancy to treat hypertension
- Many physiological changes occur in pregnancy (Figure 5) potentially altering drug pharmacokinetics
- Thus, alternative or adaptive dosing regimens are needed to ensure accurate dosing, as well as safety and efficacy outcomes
- Pregnant women are often excluded from clinical trials due to ethical concerns making them data sparse
- PBPK modeling is a series of mathematical equations that estimate the pharmacokinetics of drugs in real time for dynamically changing life-stages such as pregnancy
- However, labetalol is a 50% protein bound, multi-enzyme, multi-stereoisomeric drug, which poses some challenges in life stage PBPK model development
- Labetalol clearance is mainly through glucuronidation via UGT metabolism and changes in UGT metabolism in pregnancy are still not fully elucidated

### Materials

- To evaluate the influence of various physiological changes on labetalol PK using minimalistic life-stage PBPK model
- To implement drug and model-based sensitivity analysis of the PBPK model to identify sensitive parameters that influence overall changes in pregnancy-related drug exposure
- To quantify the contribution of the key parameters to the model output of Area Under the Curve (AUC) changes at each trimester which could aid in determining the need for greater accuracy in model assumptions from scarce data

## Materials and Methods

### Workflow

We followed the workflow below (figure 1) to obtain the normalized sensitivity coefficients (NSC) for parameters in non-pregnancy and trimester 1, 2, and 3 of pregnancy using life-stage PBPK models. NSC values for non-pregnancy and the pregnancy related changes in the influential parameters were used to calculate the contributions of each parameter to total pregnancy-related PK changes.

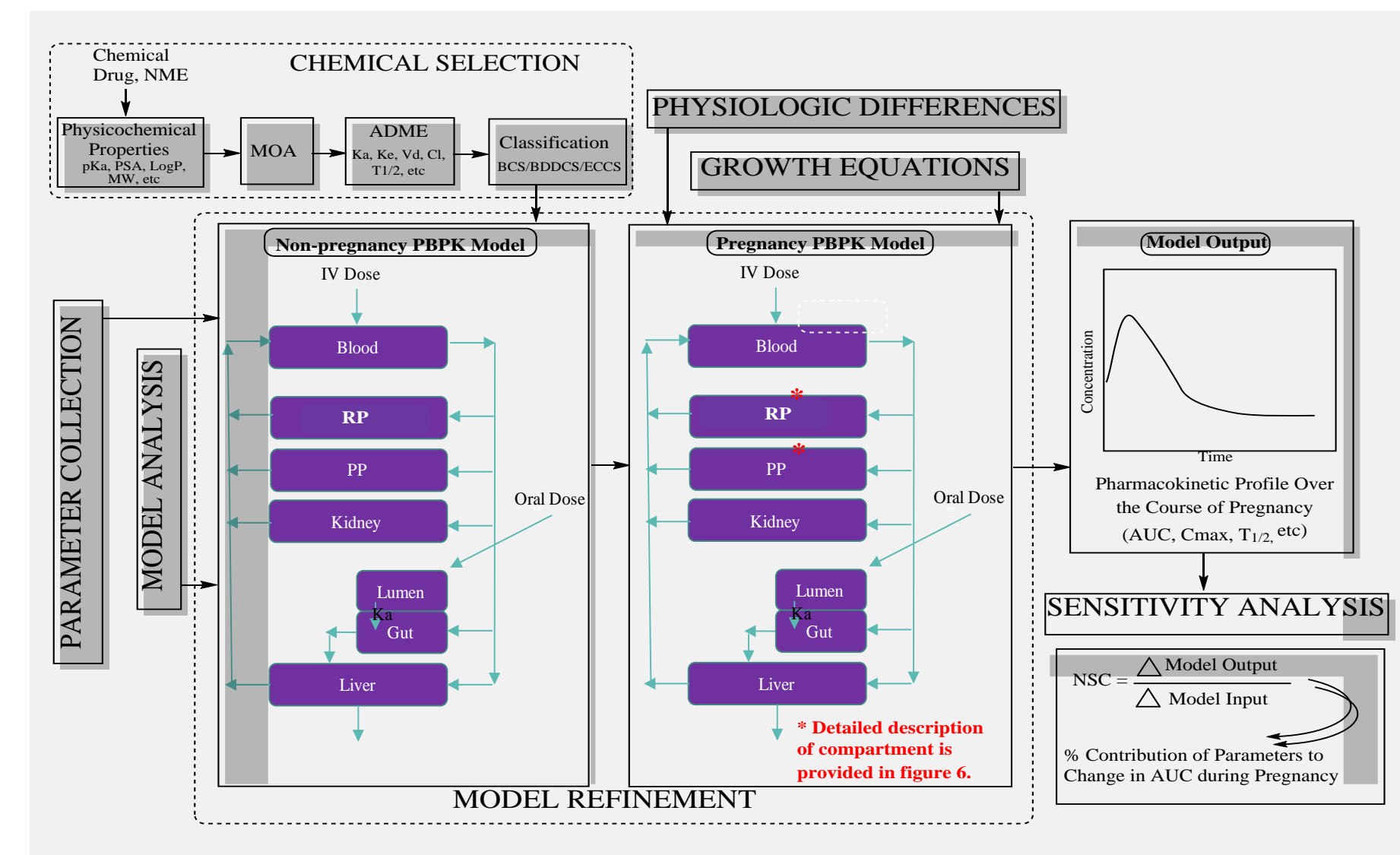


Figure 1. Structure of project workflow

### Materials

The PBPK models were constructed in Berkeley Madonna version 9.1.18. Ontogeny equations for pregnancy parameters were coded into the model to allow for real-time dependent pregnancy predictions.

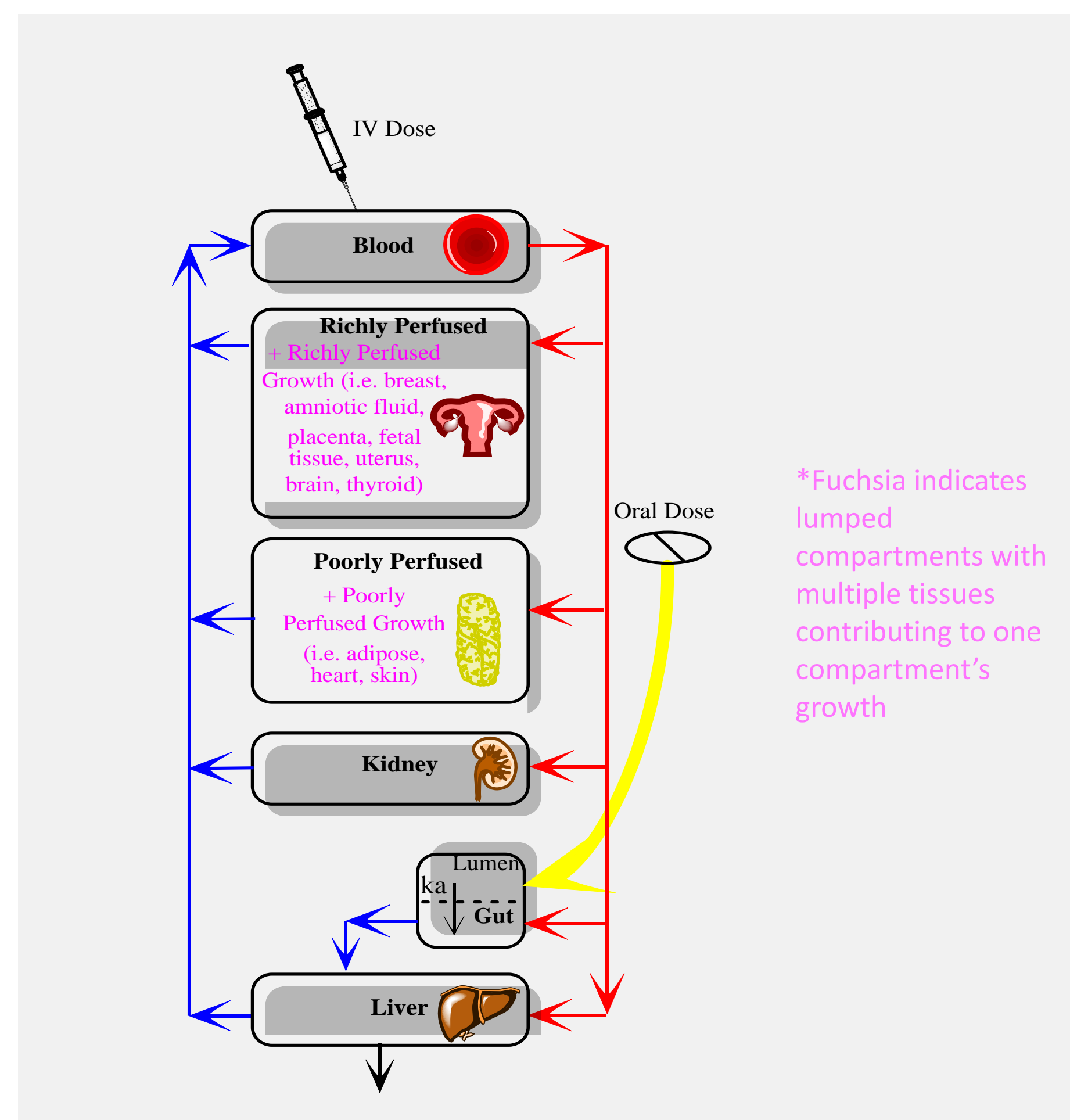


Figure 2. Full structure of minimalistic dynamic pregnancy PBPK model

## Results and Discussion

### Pregnancy Model Performance and Simulation

- The pharmacokinetic (PK) profile for labetalol following daily dosing (figure 3 & 7) shows decreasing plasma concentration trends throughout pregnancy (figure 3a & 7a) and in greater detail in figure 3b & 7b
- Table 1 shows that life stage PBPK model capturing anatomical changes only and using a fixed non-pregnancy total body clearance reasonably predicted the overall decline in AUC with pregnancy but under predicts the clearance phase as expected
- Table 2 shows increased AUC capture when applying UGT2B7 activity assumptions

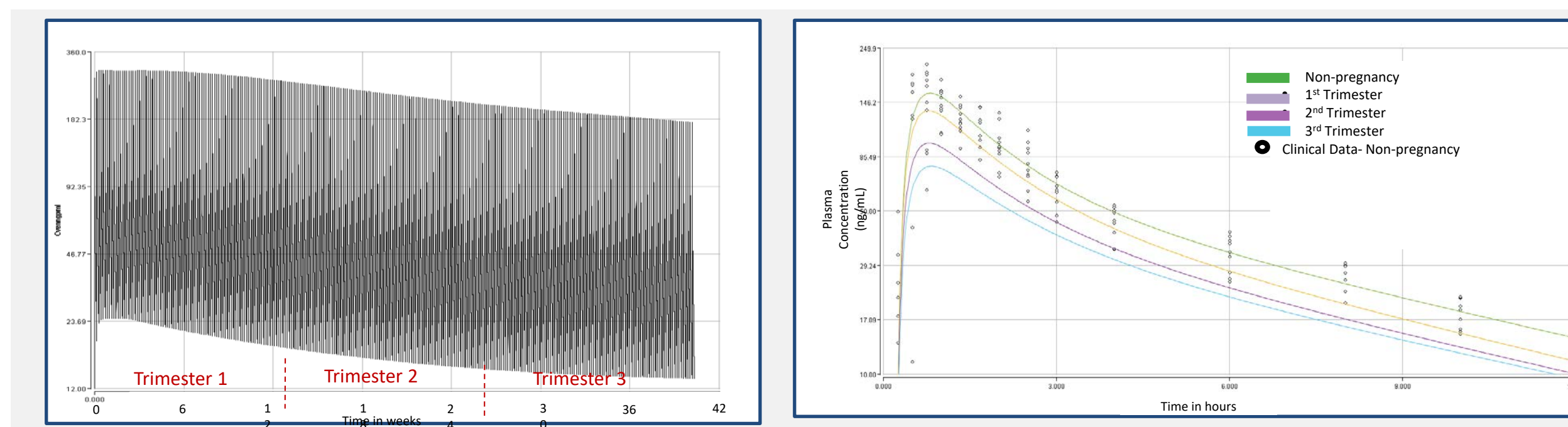


Figure 3. Simulated plasma concentration profiles of labetalol 300mg orally in a pregnant woman without UGT activity change. Left: Over 40 weeks of pregnancy from non-pregnancy to trimester 1, 2, & 3. Right: Trimesters 1, 2 & 3 and non-pregnancy superimposed on a logarithmic scale.

### Sensitivity Analysis

- The NSC is described in figure 1. A NSC value of 0.2 indicates that a 10% change in model input results in a 2% change in model output
- Sensitive parameters (NSC >0.2) with predicted greatest AUC change were body weight (1.2), albumin (0.8), and liver blood flow (0.7-0.8) in all trimesters (figure 5)

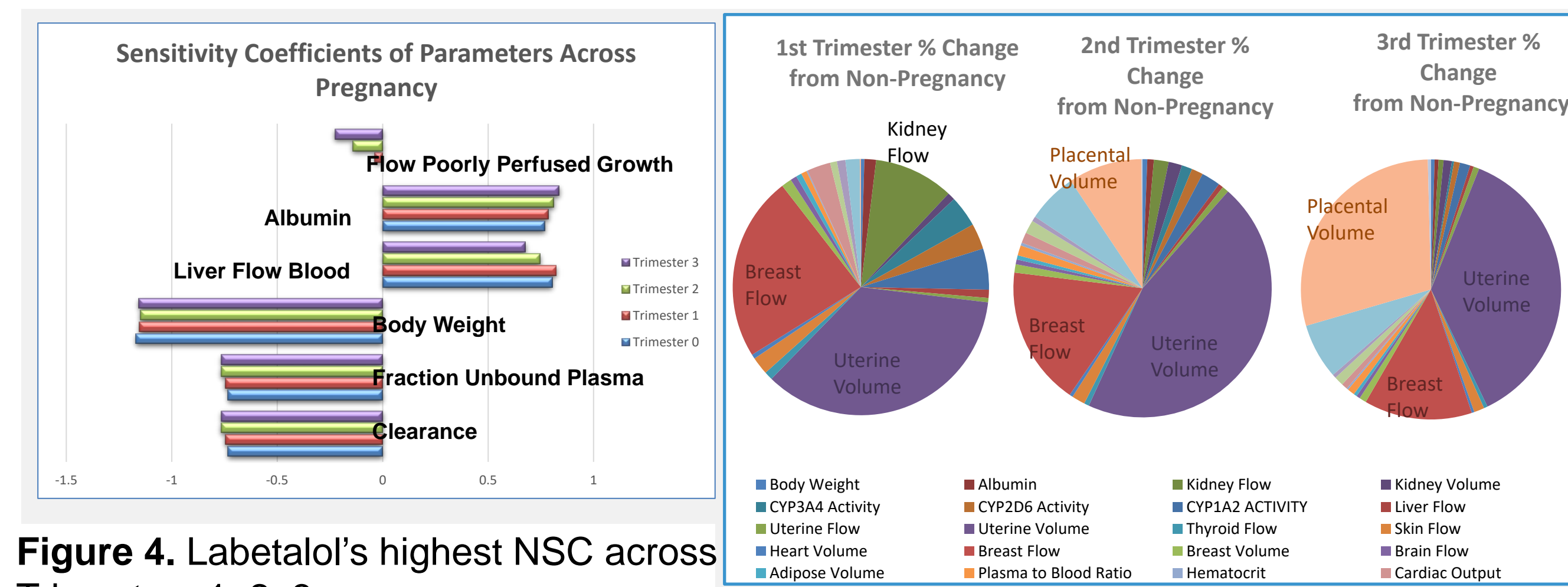


Figure 4. Labetalol's highest NSC across Trimesters 1, 2, 3.

### Contribution Analysis

- Contribution analysis was conducted using sensitivity analysis results & percent change of individual parameters at specific pregnancy time points
- The greatest contributors to trimester-specific AUC change from a baseline non-pregnancy AUC were albumin (56%, 41%, and 29%), body weight (25%, 42%, and 37%), and cardiac output (14%, 9%, and 7%) respectively
- Body weight became a greater contributor over the pregnancy (lipophilic ->increased adipose->increased Vd and high partition coefficients)
- Contribution of protein binding to AUC declined over pregnancy (moderate protein binding and decreasing albumin levels)

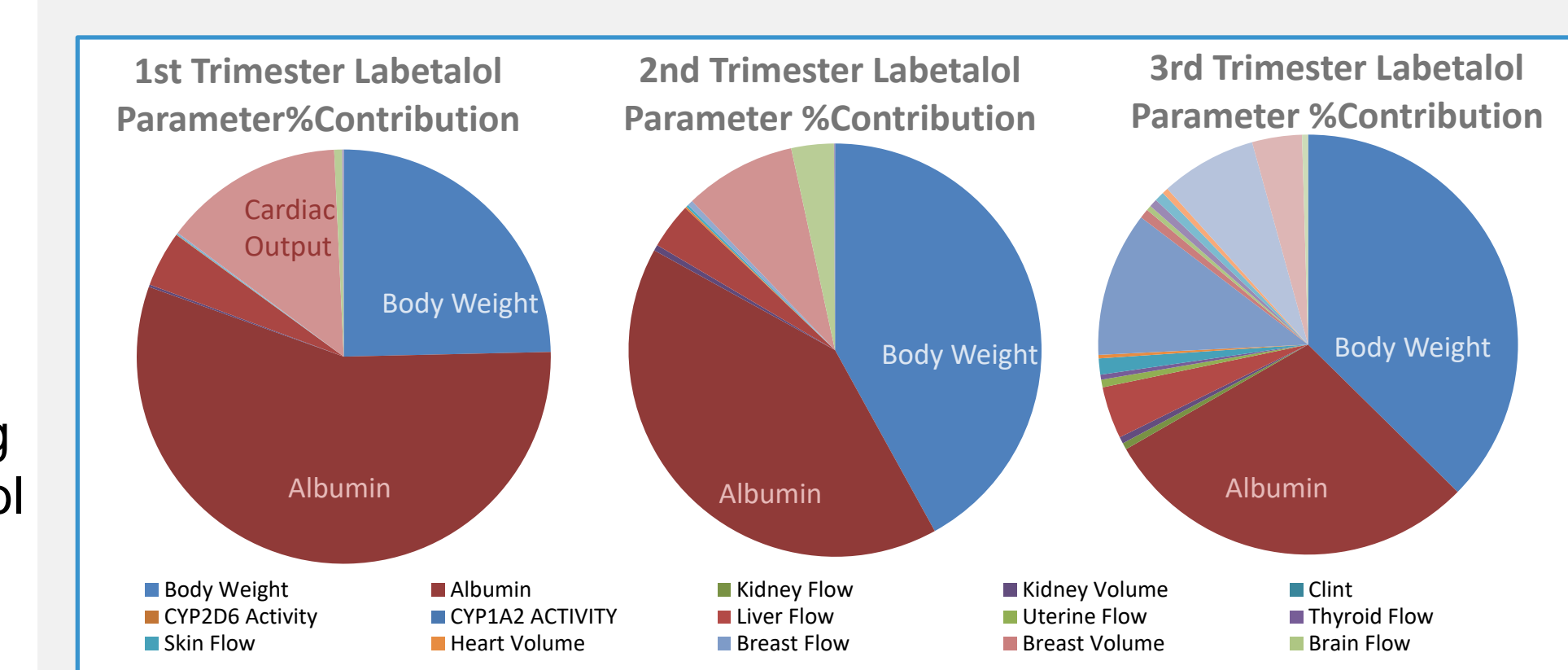


Figure 5. Parameter contributions in predicting AUC changes for labetalol across trimesters 1, 2, 3.

	Cl/F fold change	% drop in observed AUC	PBPK model predicted % drop in AUC	Uncaptured AUC	Captured AUC
Trimester 1	1.4	28.5%	16.2%	43.3%	56.7%
Trimester 3	1.6	37.5%	41.8%	11.5%	88.5%

Table 1. Model predictions compared to AUC calculated from clinically observed CL/F. 300mg Orally every 12 hours. No change in clearance from non-pregnancy input.

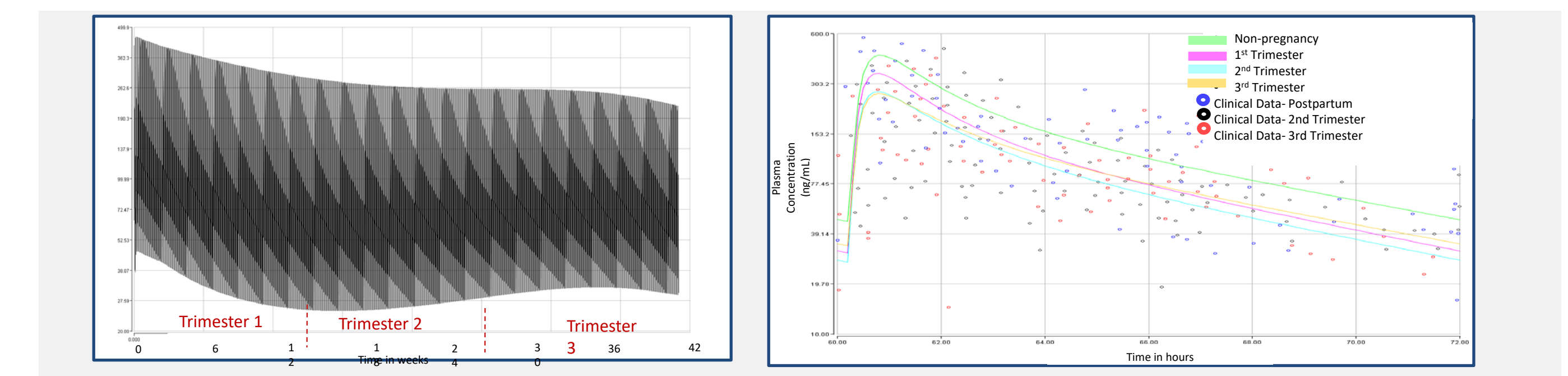


Figure 7. Simulated plasma concentration profiles of labetalol 300mg orally in a pregnant woman with UGT activity change. Left: Over 40 weeks of pregnancy from non-pregnancy to trimester 1, 2, & 3. Right: Trimesters 1, 2 & 3 and non-pregnancy superimposed on a logarithmic scale.

Figure 8. Proposed quantitative activity changes throughout pregnancy of UGT1A1 and UGT2B7.

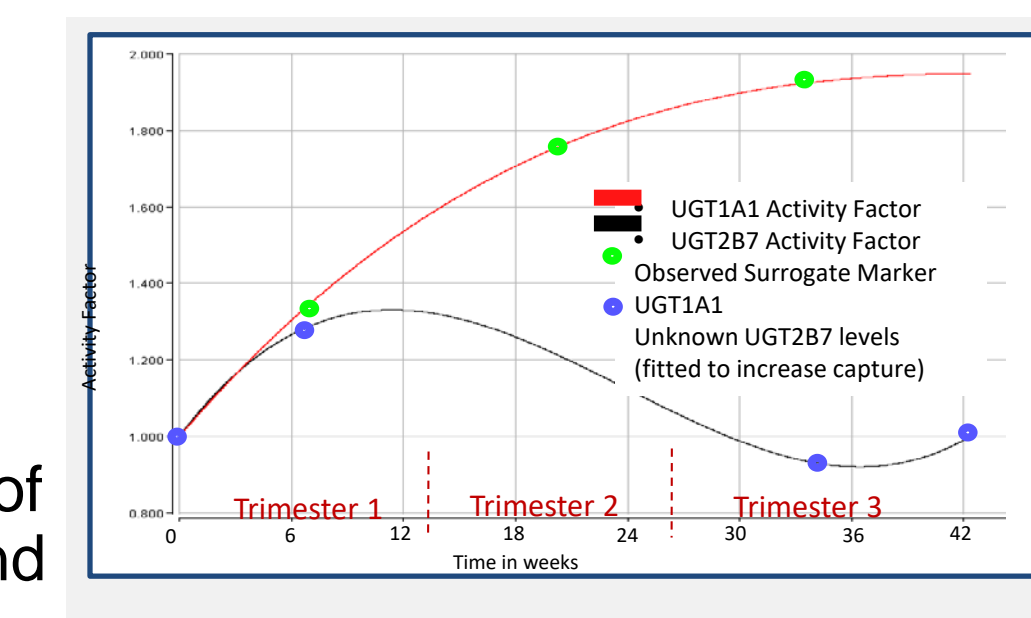
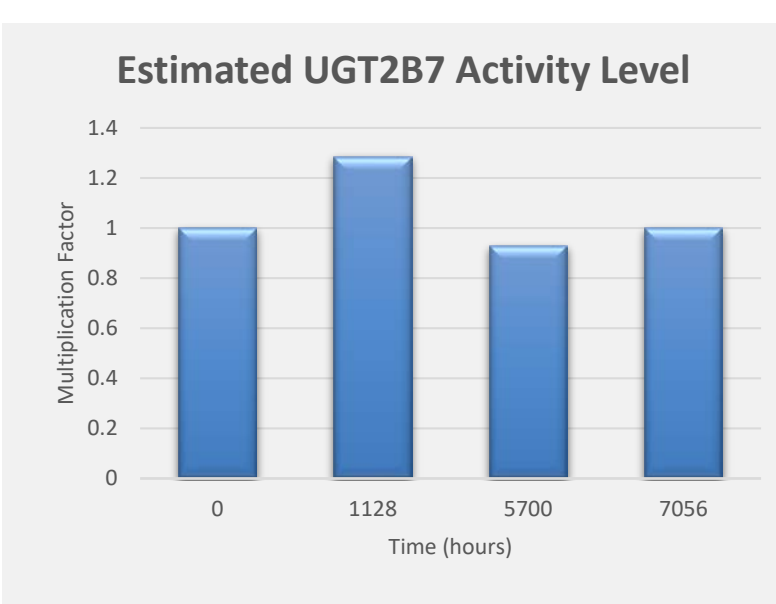


Figure 9. Proposed point activity changes to UGT2B7 for increased capture of AUC Percent change in pregnancy.



	Cl/F fold change	% drop in observed AUC	PBPK model predicted % drop in AUC	Uncaptured AUC	Captured AUC
Trimester 1	1.4	28.6%	28.6%	0.0%	100.0%
Trimester 3	1.6	37.5%	37.4%	0.2%	100.2%

Table 2. Model predictions compared to calculated AUC from clinically observed CL/F. 300mg Orally every 12 hours. UGT1A1 and UGT2B7 estimated changed included.

## Conclusion

- The life-stage PBPK model initially captured 60-90% of the total AUC changes at for trimesters 1 & 3 with the remaining possibly attributed to pregnancy related changes in UGT-mediated clearance capturing 100%.
- Progesterone influence of UGT1A1 allowed for greater certainty in the estimated equation, whereas UGT2B7 was estimated to increase AUC capture in trimesters with reported PK values available for comparison.
- Sensitivity coefficient guided parameter contribution analysis identified the primary physiological determinants of pregnancy PK for labetalol and quantified the extent of their contributions.
- Such contribution analysis could help determine the confidence of life-stage model predictions, especially in data sparse life-stages, where there are uncertainties in model input parameters and help prioritize parameterization of life-stage PBPK models in the future.

## Funding & Disclaimer

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- The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy.