

Prediction of maternal and fetal exposure to escitalopram, sertraline and paroxetine by combining human ex vivo placenta perfusion data and Physiologically Based Pharmacokinetic (PBPK) modeling

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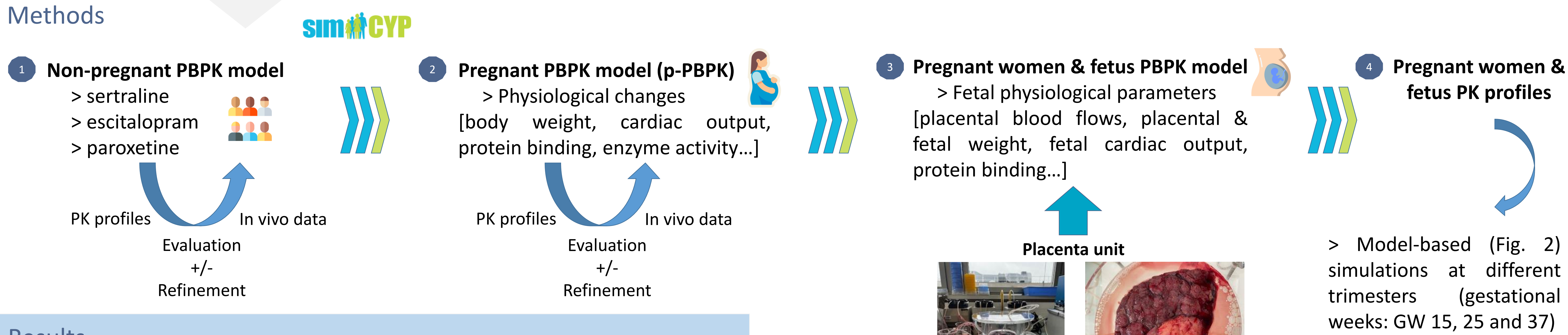


Background

Depression is common among pregnant women and selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressants during pregnancy [1].

Pregnancy is a period of significant physiological changes that affect drug pharmacokinetics (PK) [2]. To date, there is limited information on the placental transfer of antidepressants and the differences in fetal exposure between drugs are poorly characterized [3].

The aim of this study was to predict **maternal and fetal exposure** to three widely used SSRIs - **sertraline, escitalopram, and paroxetine** - across different trimesters of **pregnancy**, using a PBPK model combined with ex vivo data.



Results

- A total of 28 placentas (10 for sertraline, 9 for escitalopram and 9 for paroxetine) were modeled using a population approach.
- A PBMP model, for which unbound maternal uptake/efflux (M_{up} , M_{eff}) and fetal uptake/efflux (F_{up} , F_{eff}) clearances were estimated, satisfactorily described the ex vivo data. An additional parameter standing for placental clearance (CL_{pl}) was also estimated for all three drugs and improved significantly the fit.
- The p-PBPK models accurately predicted **maternal** (Fig. 3) and **fetal** (Fig. 4) concentration time-courses of these SSRIs.

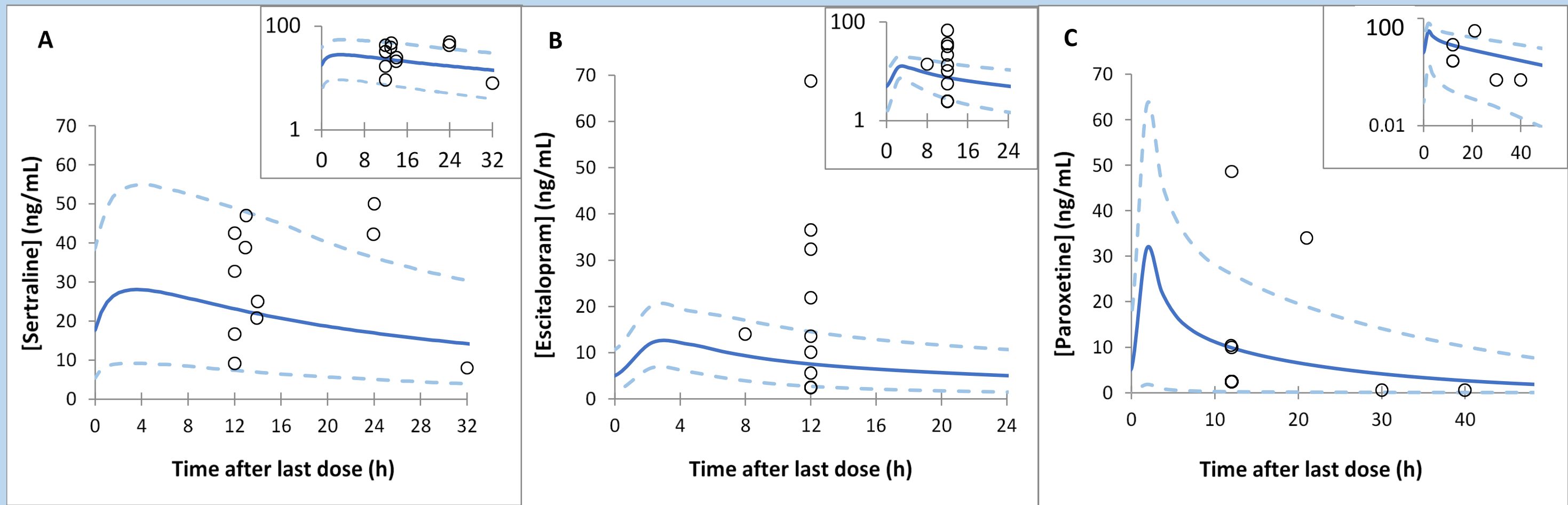


Fig. 3. Predicted maternal plasma concentration-time profiles from antidepressants PBPK models at GW 39. Predicted and observed maternal plasma concentrations of A) sertraline (100 mg daily), B) escitalopram (10 mg daily), and C) paroxetine (20 mg daily) at steady-state.

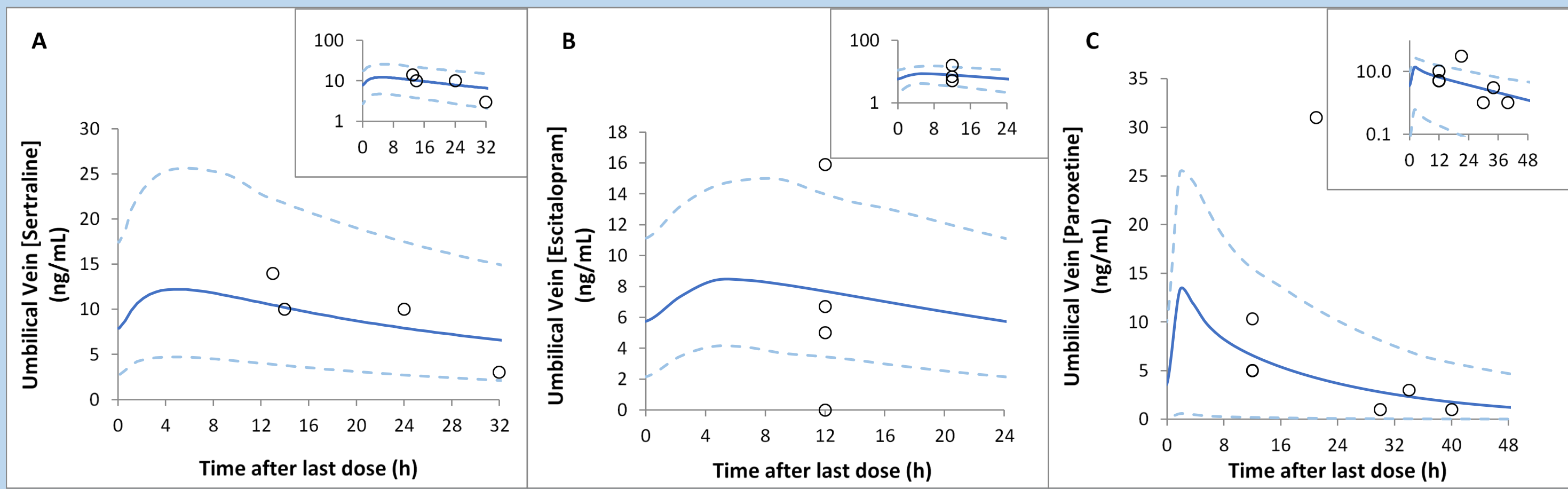


Fig. 4. Predicted umbilical vein concentration-time profiles for antidepressants at GW 39. Predicted and observed umbilical vein concentrations of A) sertraline (100 mg daily), B) escitalopram (10 mg daily), and C) paroxetine (20 mg daily) at steady-state.

Conclusions

- Overall, **sertraline** appeared to have the **lowest fetal exposure** relative to the mother while maintaining maternal concentrations within the recommended therapeutic range.
- Escitalopram** was the molecule with the **highest fetal-to-maternal exposure**.
- Finally, **paroxetine** appeared to have an **intermediate fetal-to-maternal exposure**, but a **substantial drop in maternal concentrations** was predicted.

This work confirms the benefit of integrating ex vivo human cotyledon perfusion data into PBPK modeling.

This work provides a good overview of maternal and fetal exposure trends throughout pregnancy and can serve as a starting point to support clinical decision-making and therapeutic monitoring.

References

1: Bénard-Larivière A. et al. *Br J Clin Pharmacol* (2018) 84, 1764–1775. 4: Préta L.H. et al. [Manuscript submitted for publication]. (2025).
2: Pariente G. et al. *PLoS Med* (2016) 13, e1002160.3. 5: Roelofsen D. et al. *Toxicology in Vitro* (2022) 85, 105471.
3: Zheng L. et al. *J Clin Pharmacol* (2022) 62, S115–S128. 6: Abduljalil K. et al. *Front Pediatr.* (2022) 10, 840710.

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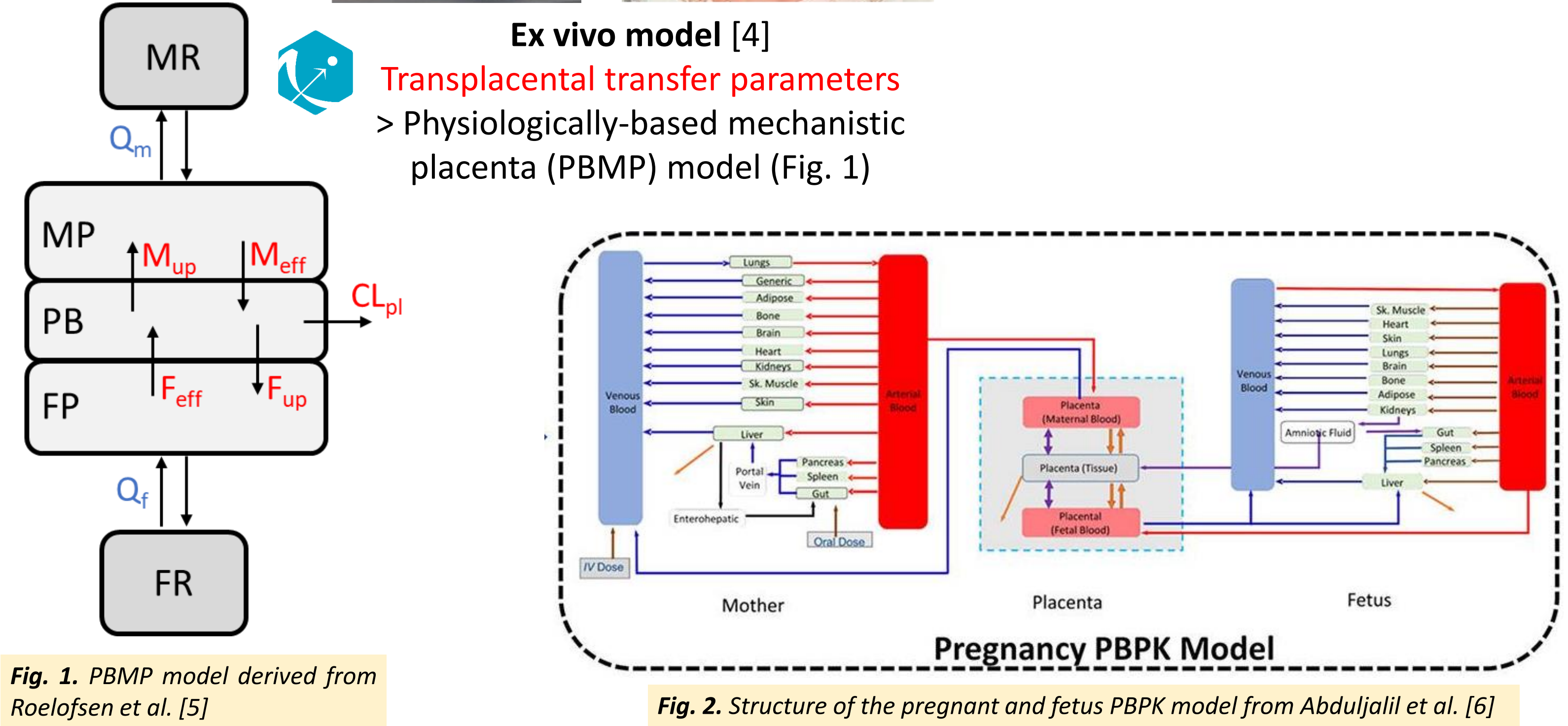


Fig. 1. PBMP model derived from Roelofsen et al. [5]

Fig. 2. Structure of the pregnant and fetus PBPK model from Abduljalil et al. [6]

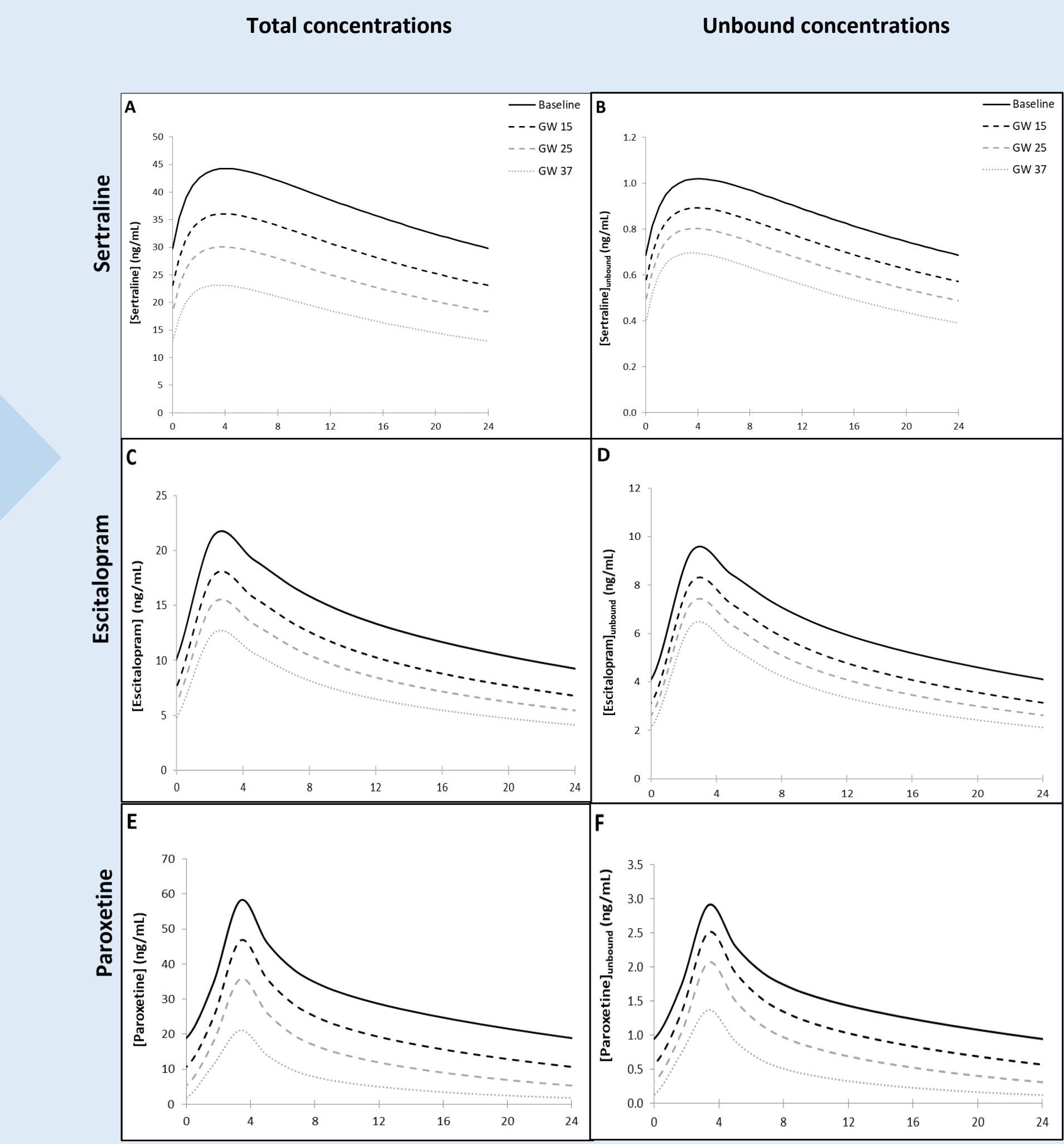


Fig. 5. Predicted maternal total and unbound concentration-time profiles of antidepressants at different gestational weeks (GW 15, 25, 37) at steady-state. Baseline corresponds to the non-pregnant period. Sertraline is given at 100 mg daily, escitalopram, 10 mg daily and paroxetine, 20 mg daily. Dotted lines represent mean concentrations predicted in the representative pregnant population.

To assess **fetal exposure** relative to the mother, **cord blood-to-maternal plasma area under curve ratios over 24 hours** (AUC_{24}) were calculated based on model predictions (Tab. 1). By the end of pregnancy, fetal to maternal AUC ratios were **0.45 for sertraline, 0.91 for escitalopram, and 0.58 for paroxetine**.

	GW (weeks)	Cord to maternal plasma AUC_{24} ratio
Sertraline	15	0.15
	25	0.32
	37	0.45
Escitalopram	15	0.57
	25	0.76
	37	0.91
Paroxetine	15	0.20
	25	0.41
	37	0.58

Tab. 1. Predicted fetal cord to maternal area under the curve ratios derived from concentration-time profiles at steady state across gestational age