Quantifying placental drug transfer with *ex vivo* cotyledon perfusion assays as PBPK input

Fetal Pharmacology & Therapeutics Workshop, 21st and 22nd of October 2021

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Isolated human cotyledon perfusion

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Ex vivo dual perfusion of an isolated cotyledon of human placenta: History and future challenges

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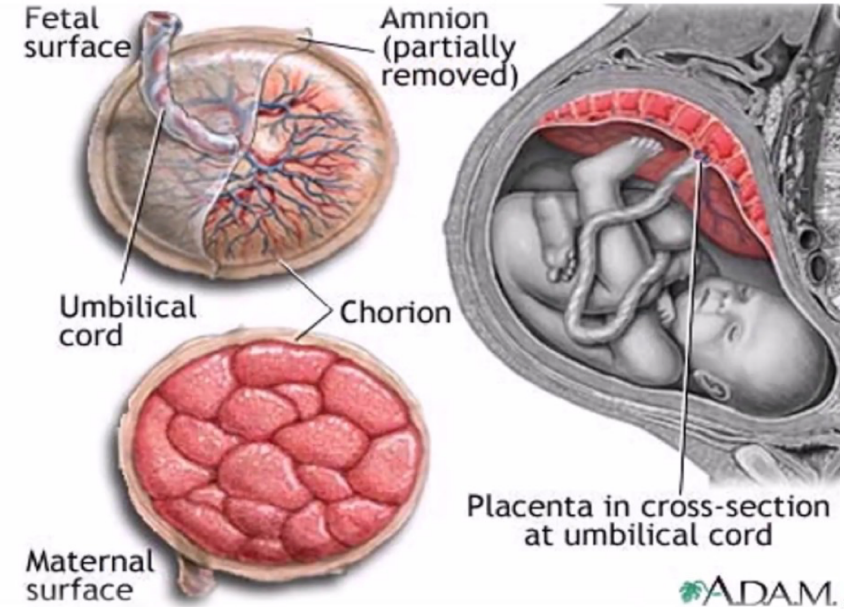
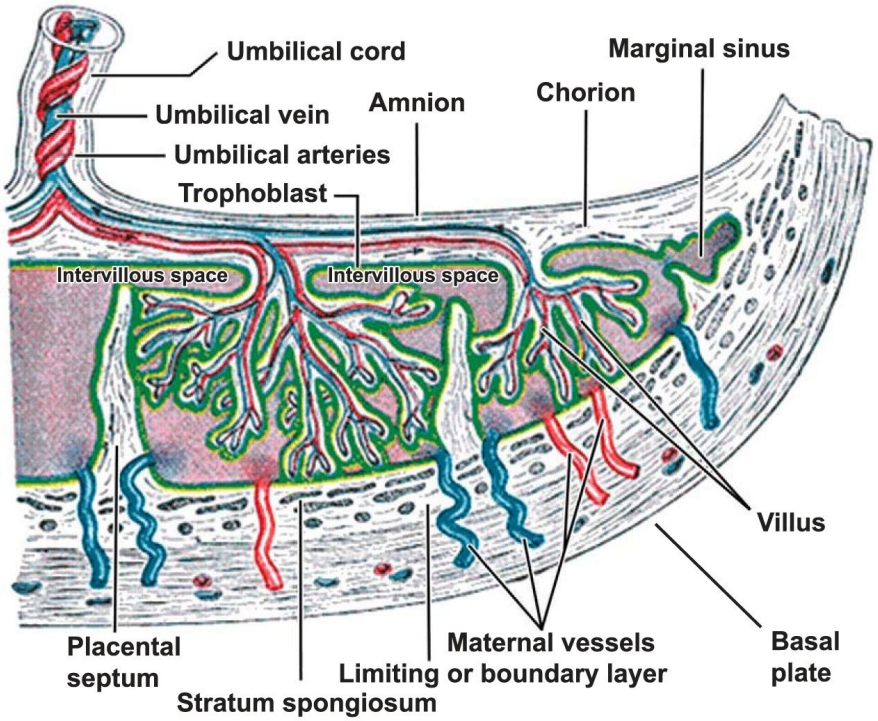
12th European Placenta Perfusion Workshop (EPPW), 2019, Nijmegen

The placenta





http://www.adameducation.com
Serov et al. J Appl Physiol 120: 17–28, 2016

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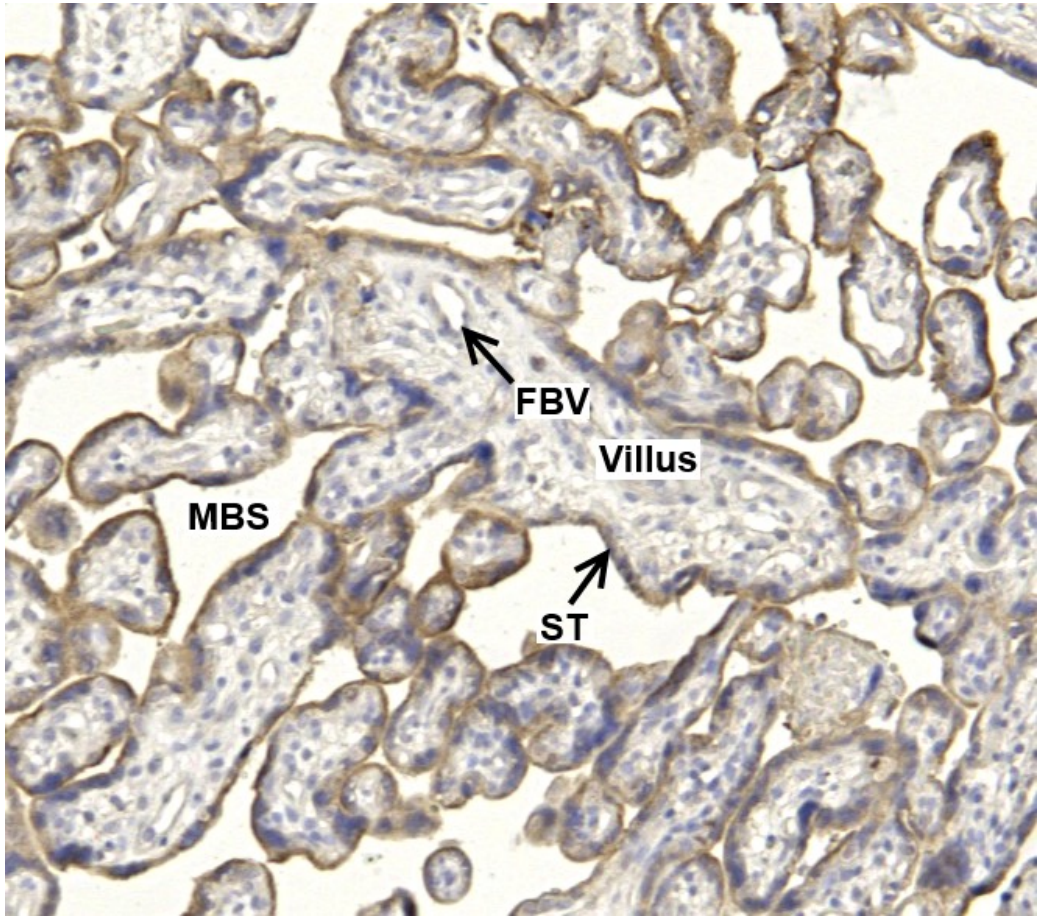
Histology

Tissue section of villous material from human placenta

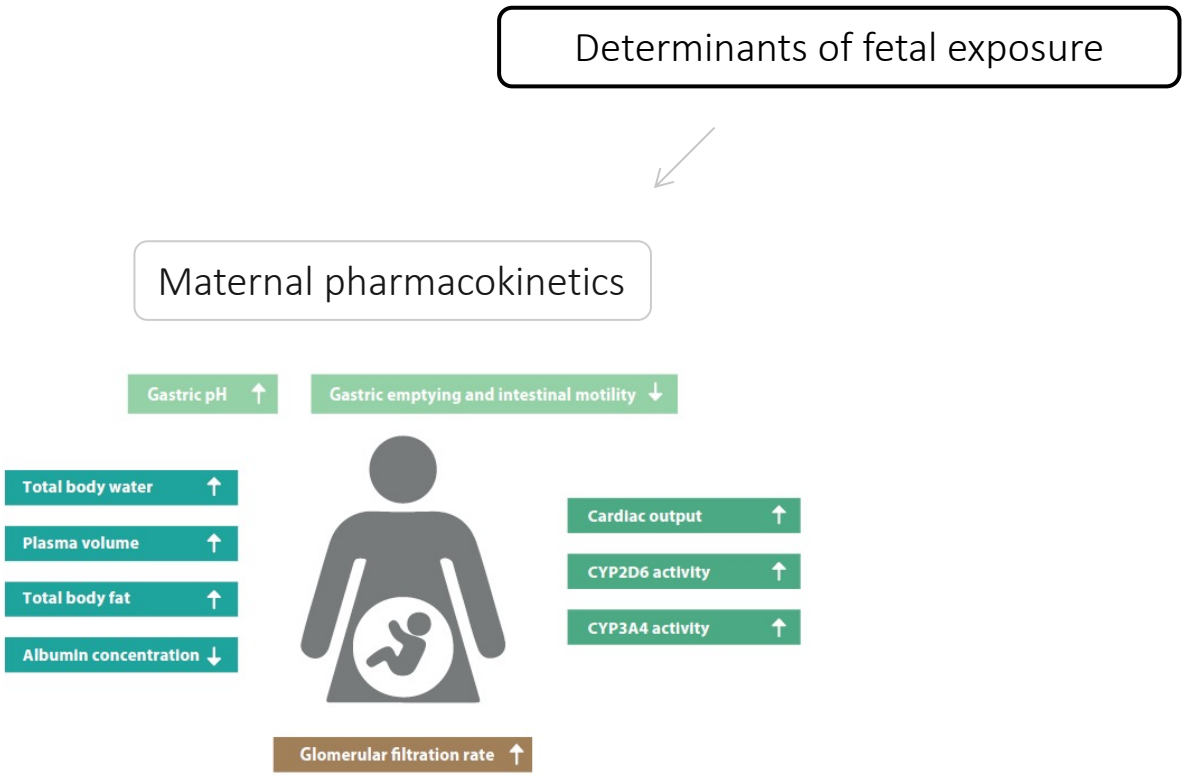


FBV: fetal blood vessel
MBS: Maternal blood space
ST: Syncytiotrophoblast layer

Brown staining: P-gp expression

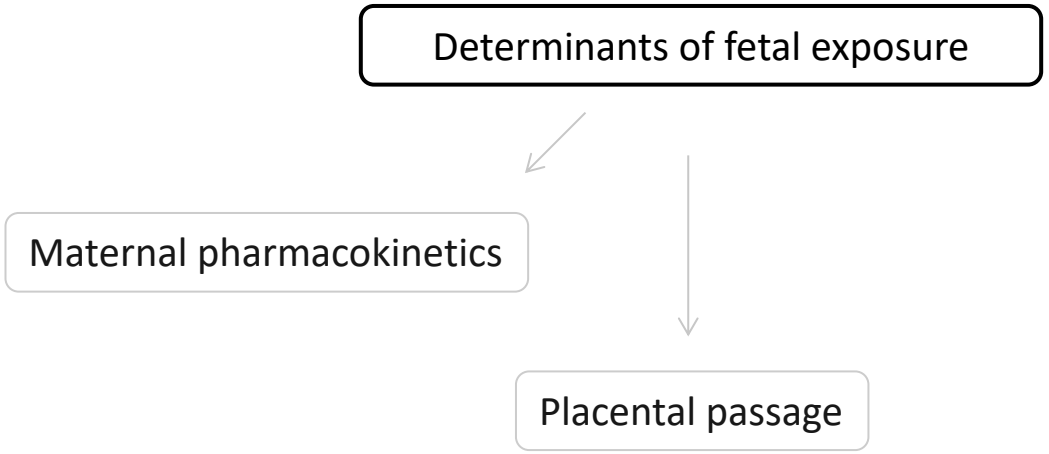
Eliesen et al. Toxicol Sci. 2017 Jun 1;157(2):500-509.

Predicting fetal drug exposure

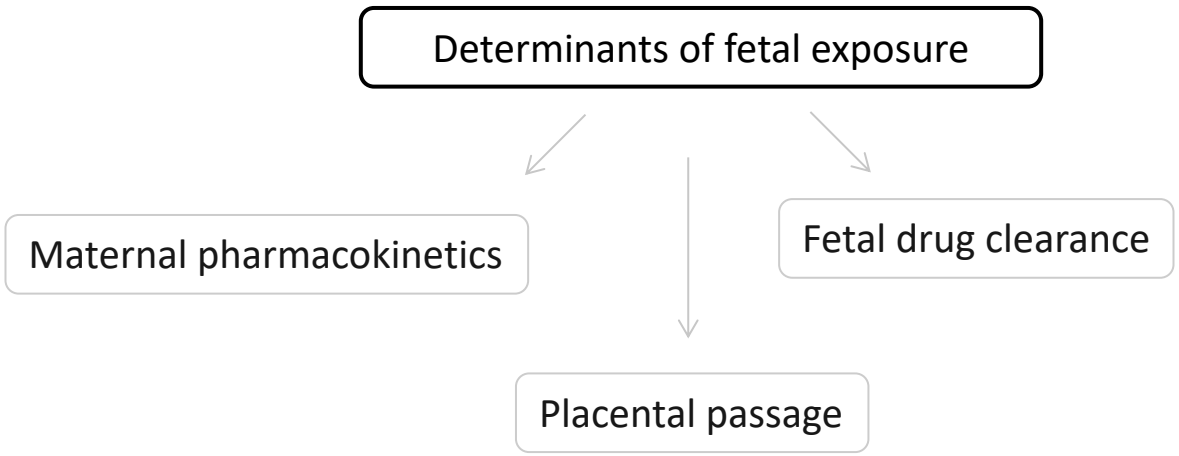


Modified from Colbers et al.

Predicting fetal drug exposure



Predicting fetal drug exposure



Anti-retroviral therapy during pregnancy

Clin Pharmacol Ther. 2020 Jun;107(6):1352-1361. doi: 10.1002/cpt.1748. Epub 2020 Jan 24.

Assessment of Maternal and Fetal Dolutegravir Exposure by Integrating Ex Vivo Placental Perfusion Data and Physiologically-Based Pharmacokinetic Modeling

Jolien J M Freriksen [1 2], Stein Schalkwijk [2], Angela P Colbers [2], Khaled Abduljalil [3], Frans G M Russel [1], David M Burger [2], Rick Greupink [1]

Around 1.4 million HIV-infected women give birth every year

Antiretroviral therapy reduces HIV transmission chance to **<2%**

Stepwise approach

1.

Maternal exposure to dolutegravir during pregnancy

→ Simulate maternal plasma concentrations via PBPK modelling (Simcyp / Berkeley Madonna)

2.

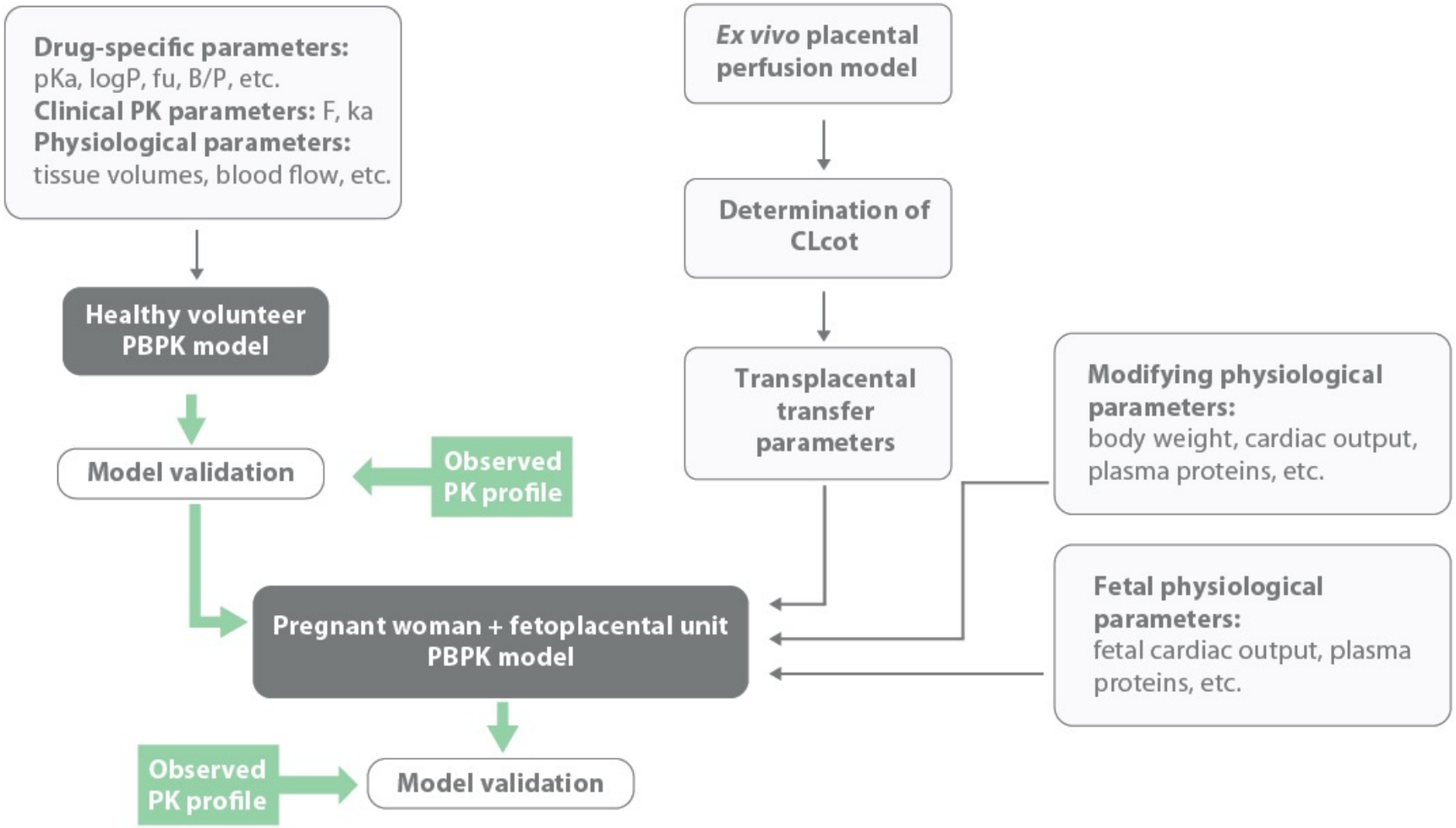
Fetal exposure to dolutegravir

→ Perform *ex vivo* placental perfusion experiments (term placenta)

↓

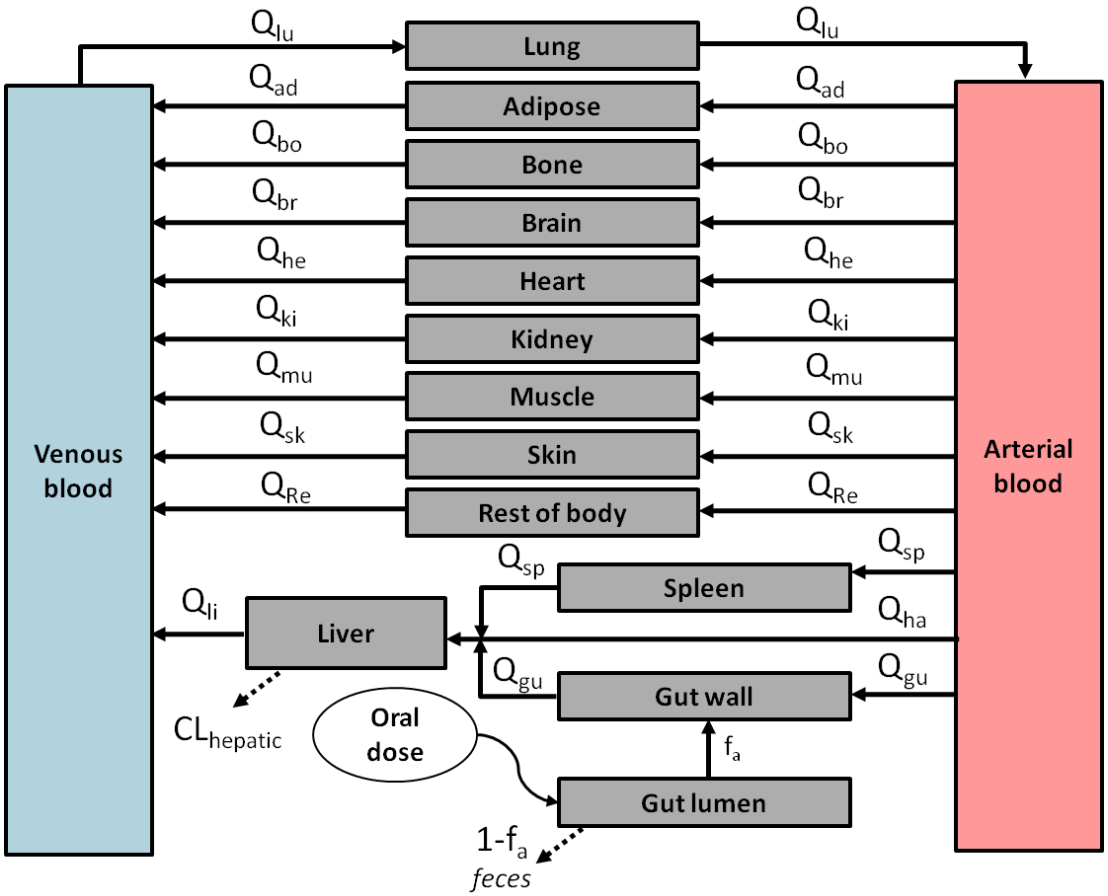
Incorporate transport data into p-PBPK model and simulate fetal plasma concentrations

Stepwise approach



Freriksen et al. Clin Pharmacol Ther. 2020 Jun;107(6):1352-1361

Create a PBPK model for non-pregnant women

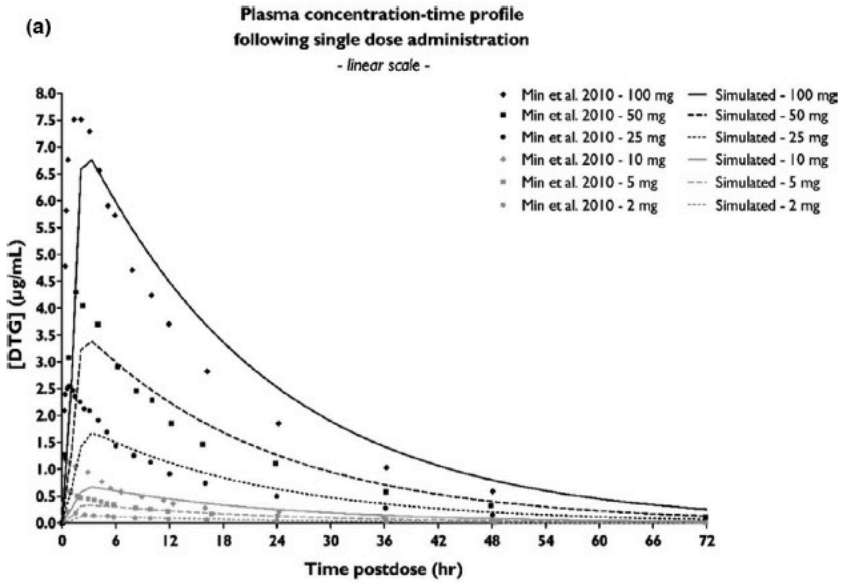


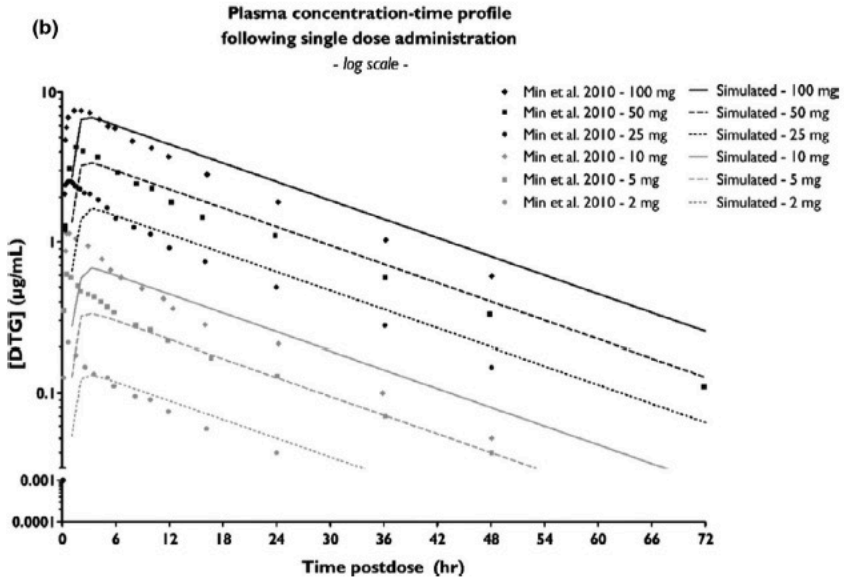
SIMCYP

Berkeley Madonna

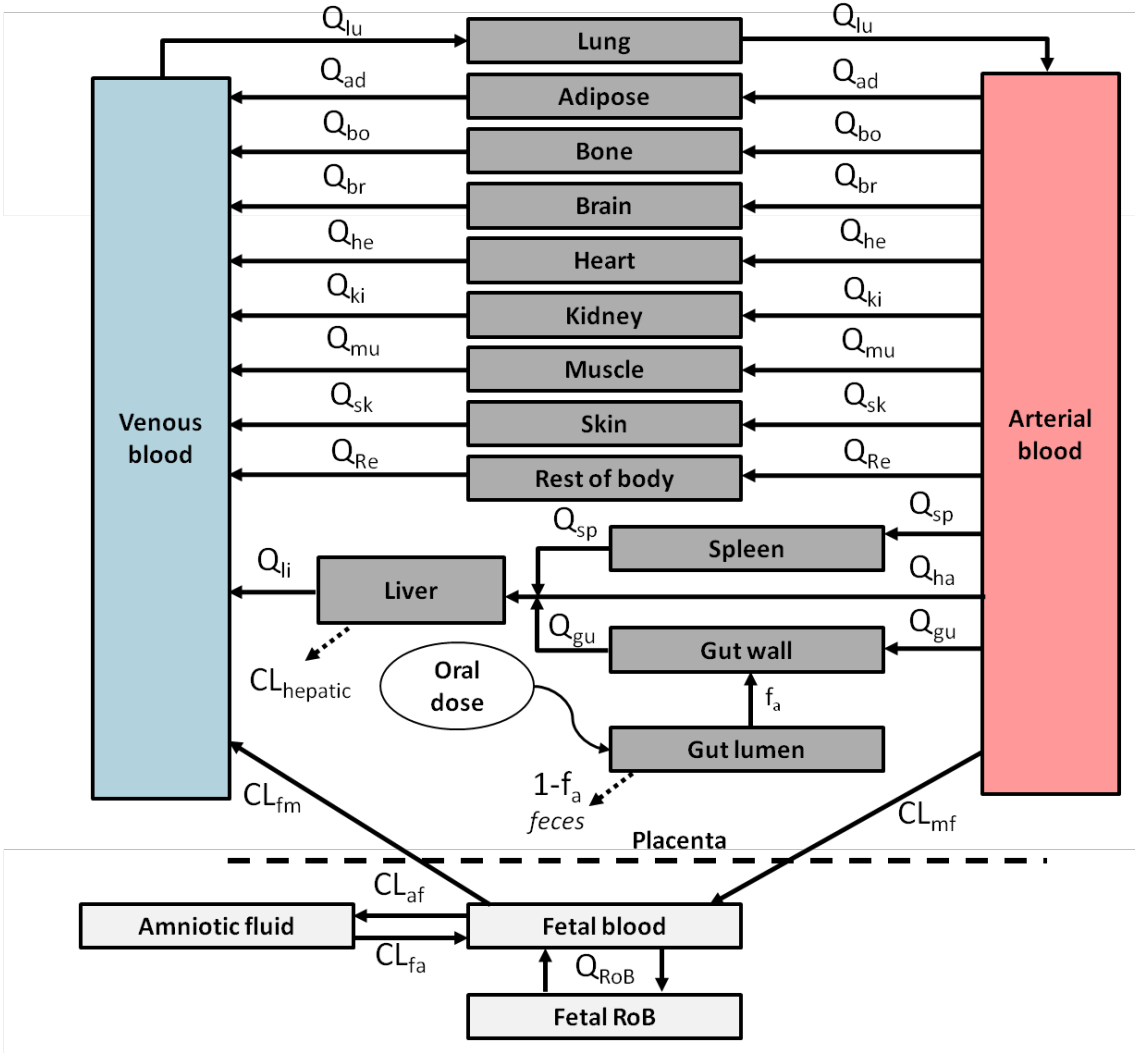
Freriksen et al. Clin Pharmacol Ther. 2020 Jun;107(6):1352-1361

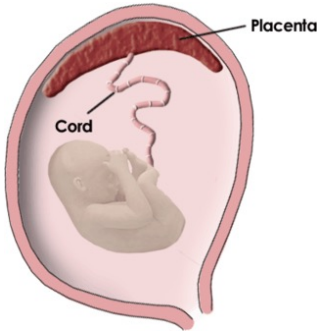
Simulated vs Clinical PK (non-pregnant)





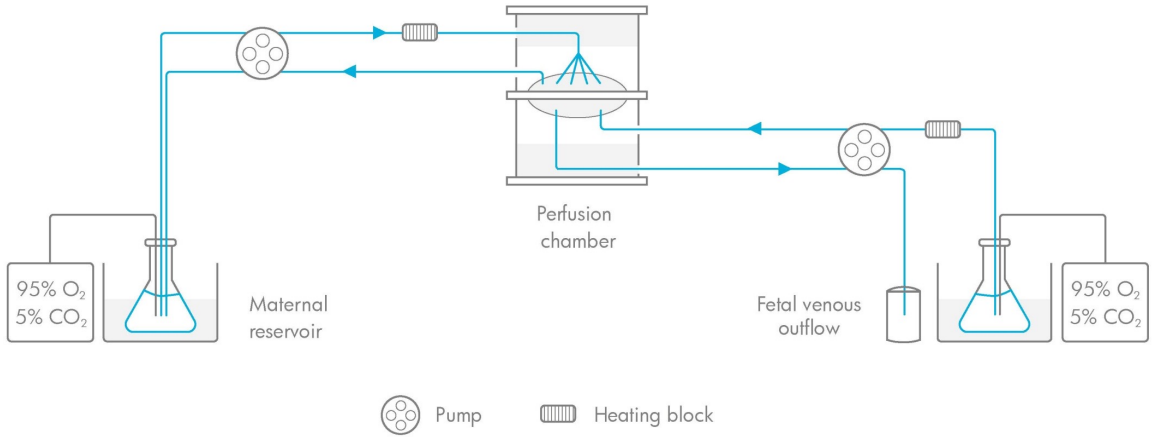
Create a pregnancy-PBPK model





Freriksen et al. Clin Pharmacol Ther. 2020 Jun;107(6):1352-1361

Isolated human cotyledon perfusion



Maternal circulation	Foetal circulation
Krebs buffer (pH 7.4)	Krebs buffer (pH 7.4)
Albumin (30 g/L)	Albumin (30 g/L)
Antipyrine (100 mg/L)	FITC-dextran (36 mg/L)
95% O_2 5% CO_2	95% O_2 5% CO_2
Flow: 12 mL/min	Flow: 6 mL/min

3 hour placenta perfusions
(small molecules)

Maternal circulation	Foetal circulation
RPMI (pH 7.4)	RPMI (pH 7.4)
Albumin (29 g/L)	Albumin (34 g/L)
Antipyrine (100 mg/L)	
95% O_2 5% CO_2	95% N_2 5% CO_2
Flow: 12 mL/min	Flow: 6 mL/min

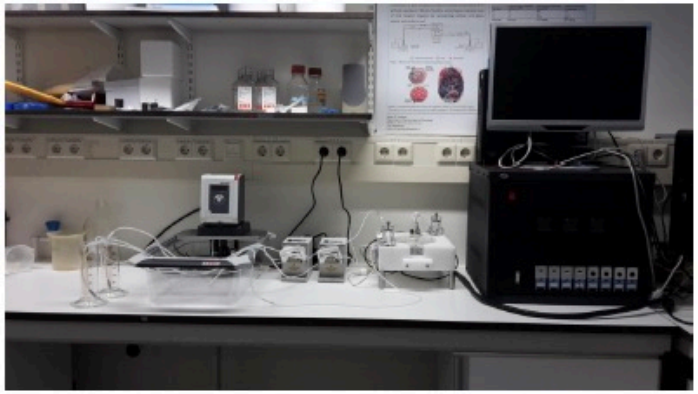
6 hour placenta perfusions
(biologics)

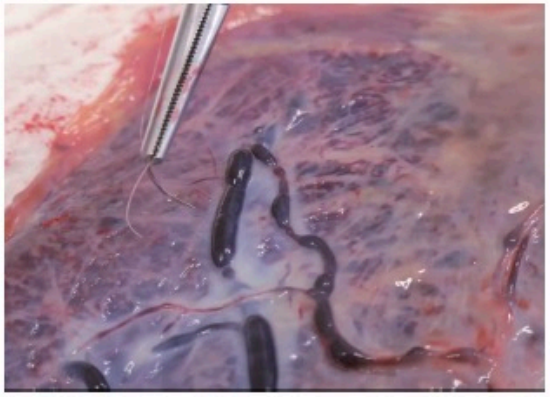
Eliesen et al. Clin Pharmacol Ther. 2020 Jul;108(1):99-106.

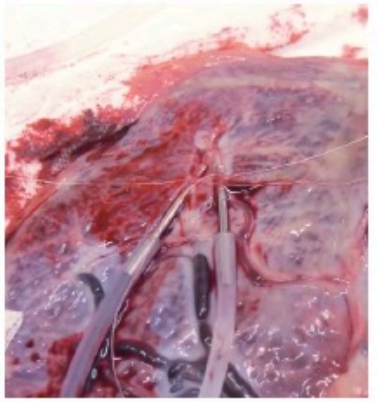
Eliesen et al. Toxicol Sci. 2017 Jun 1;157(2):500-509.

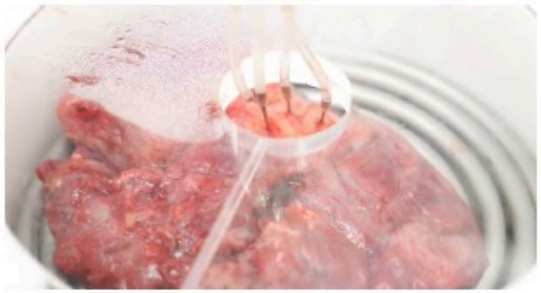
Freriksen et al. Clin Pharmacol Ther. 2020 Jun;107(6):1352-1361

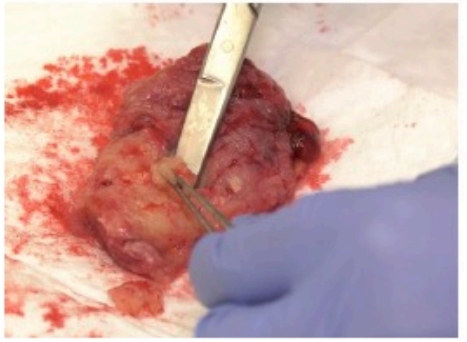
Isolated human cotyledon perfusion



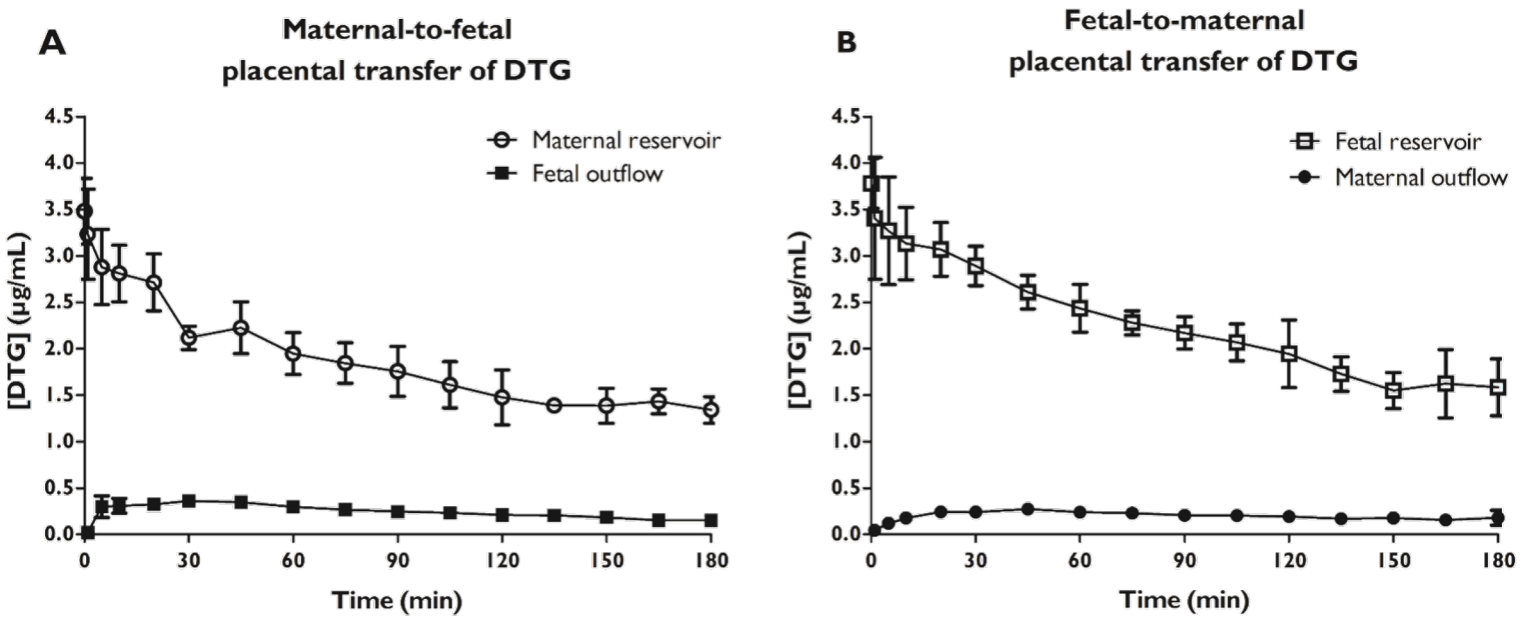








Placental transfer *ex vivo*



Clearance values (mean ± SD):

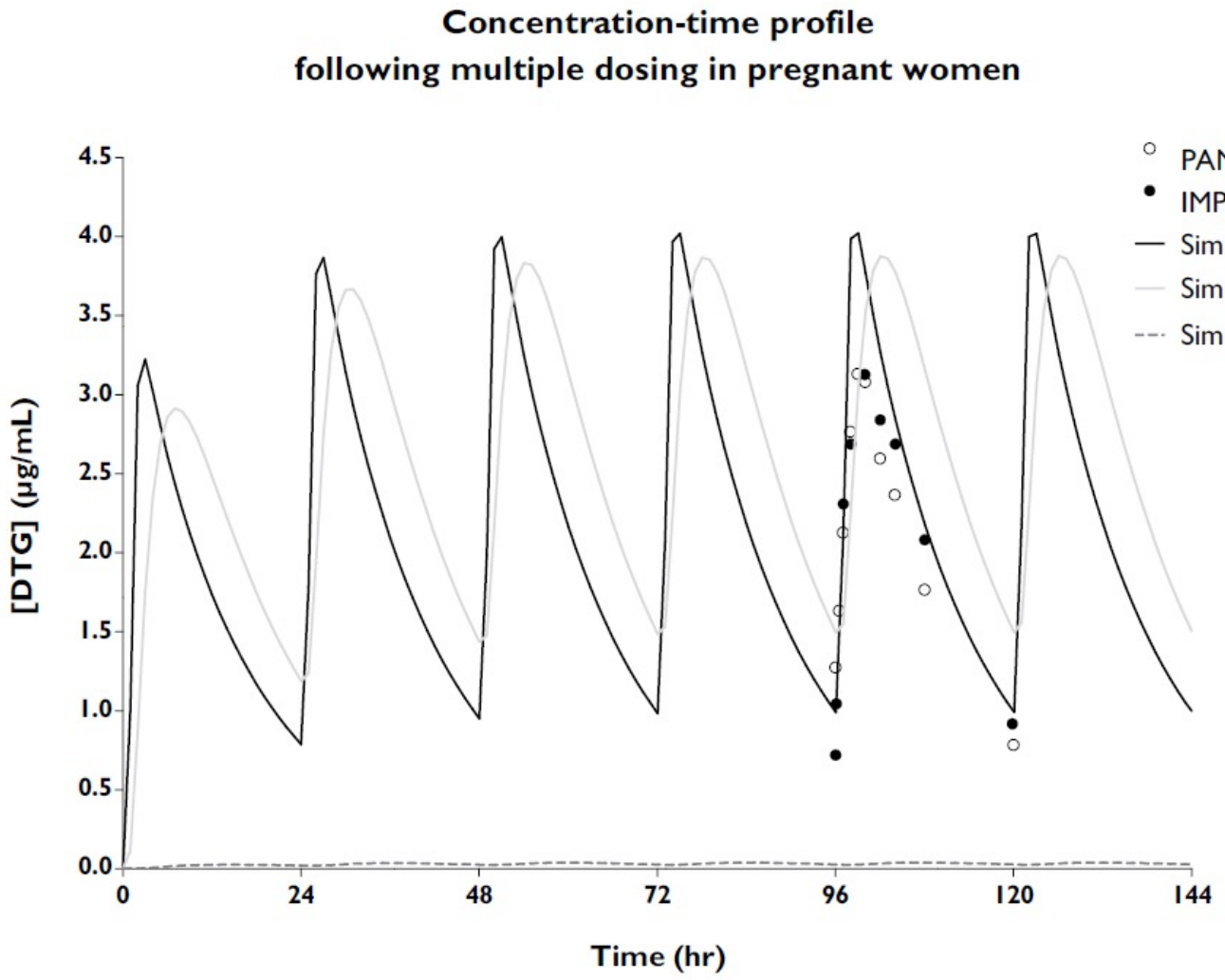
1.03 ± 0.06 mL/min

1.03 ± 0.23 mL/min

- Clearance was then corrected for protein binding in maternal and fetal perfusates
- Clearance was scaled from 1 perfused cotelydon to whole placenta
- Used for parameterization of the p-PBPK model

Freriksen et al. Clin Pharmacol Ther. 2020 Jun;107(6):1352-1361

Predicted maternal and fetal exposures



Cord blood-to-maternal blood concentration ratio

Simulated:
0.57 – 1.51

Observed:
0.64 – 1.81

Freriksen et al. Clin Pharmacol Ther. 2020 Jun;107(6):1352-1361

Conclusion

- The human cotyledon perfusion technique can be used to generate *ex vivo* placental transfer data in the term/3rd trimester placenta.

- The data can be successfully used for parameterization of pregnancy PBPK models.

- The model allows for an integrated assessment of passive and active transport in both directions across the placental barrier.

- Human system in which all placental celltypes are present in their physiological context.

- *In vitro-to-in vivo* scaling is straightforward (based on cotyledon weight or cotelydon number).

- Allows for assessment of interindividual variation in placental transfer / perform studies in placentas obtained from patients with specific morbidities.

Thank you for your attention!

Funding:

Certara/Simcyp

Bill & Melinda Gates Foundation