PBPK Modeling Approach in Pregnant Subjects and Fetus

Webinar: Wednesday, September 29th

5 PM CEST (Paris) / 8 AM PDT (Los Angeles) / 11 AM EDT (New York)

Maxime Le Merdy

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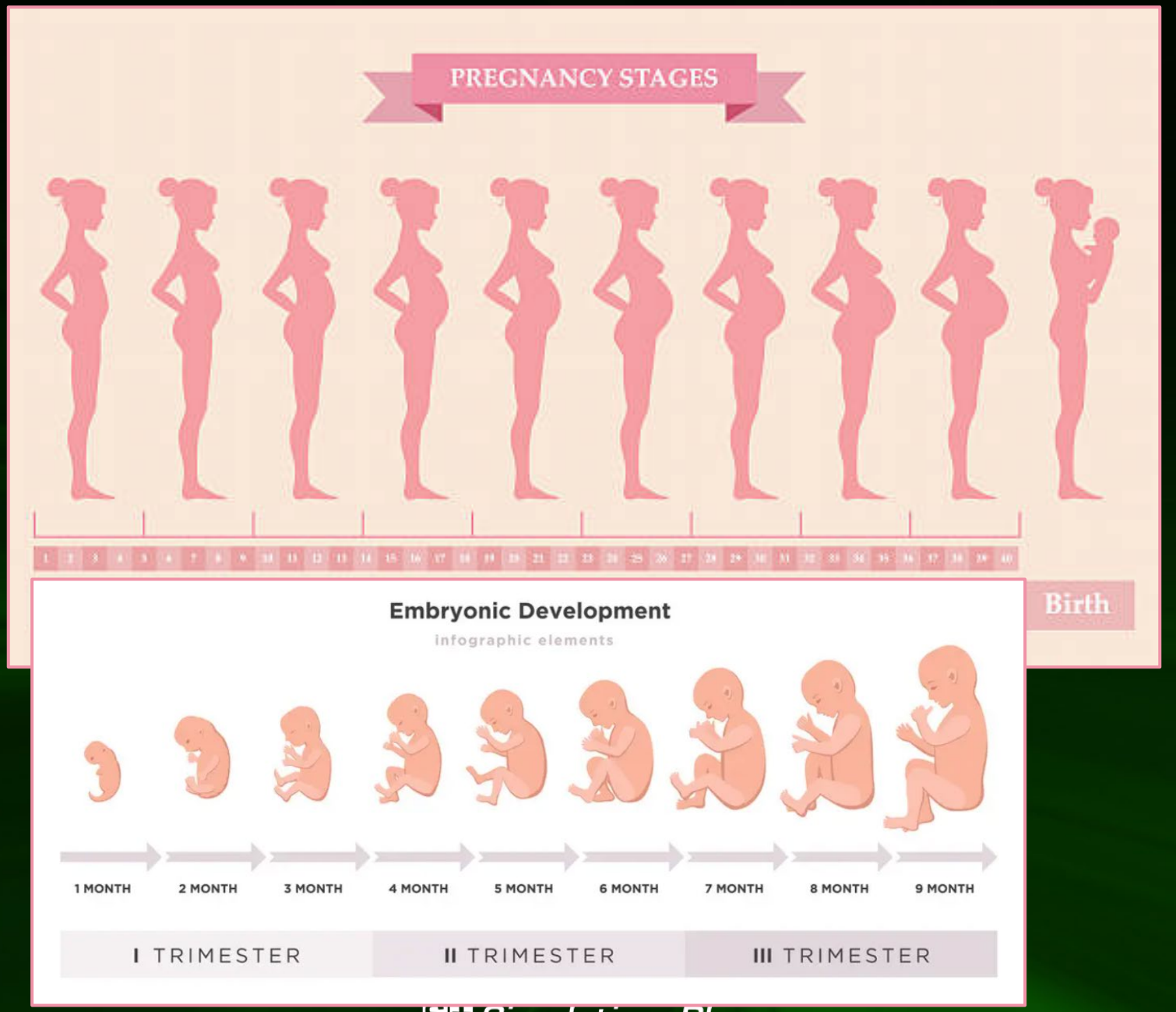

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Guidance for Industry

Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling

FDA, 2004

"Introduction to population PK modeling approaches"

"PK studies including pregnant patients, **physiological changes** during and after pregnancy **that are critical for drug absorption and disposition** may need to be considered in the model."

Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials

Guidance for Industry

FDA, 2018

EMA, 2006

GUIDELINE ON

THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY:

NEED FOR POST-AUTHORISATION DATA

EMA, 2009

GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING

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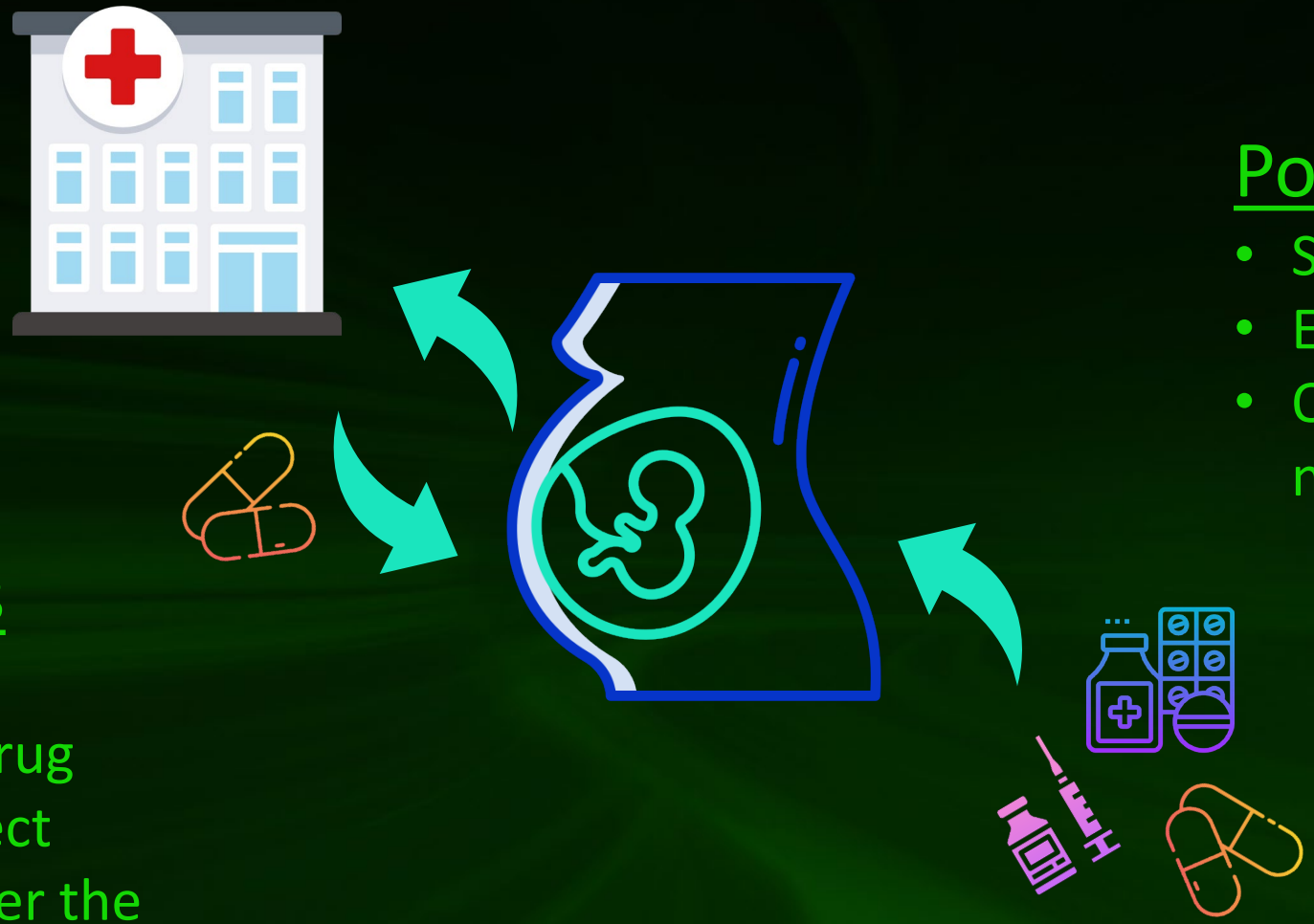
Pregnant women clinical information



Clinical Trials

- Safe
- Ethical if the drug provides a direct benefit to either the mom or the fetus

Post-marketing

- Safety concerns
- Ethical limitations
- Other approaches are necessary

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Paracetamol

Paracetamol is considered safe to use at all stages of pregnancy by physicians and pharmacist ….

… and yet:

OPEN

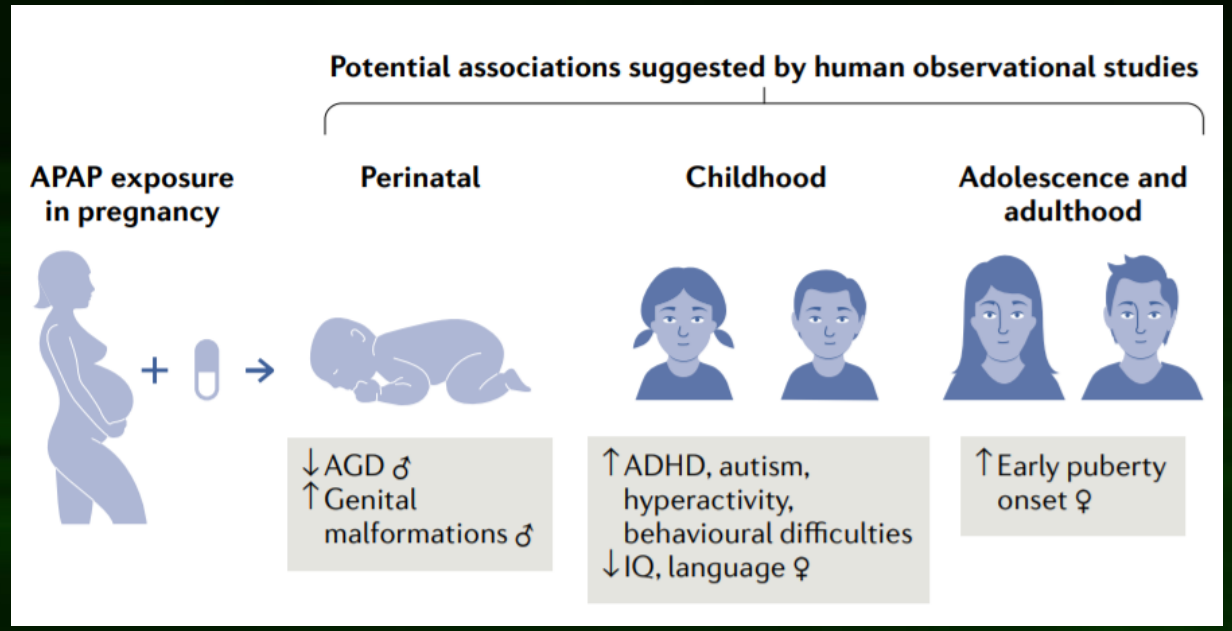
Check for updates

Paracetamol use during pregnancy — a call for precautionary action

Ann Z. Bauer[1], Shanna H. Swan[2], David Kriebel[1], Zeyan Liew[3], Hugh S. Taylor[4], Carl-Gustaf Bornehag[2,5], Anderson M. Andrade[6], Jørn Olsen[7], Rigmor H. Jensen[8], Rod T. Mitchell[9], Niels E. Skakkebaek[10], Bernard Jégou[11,13] and David M. Kristensen[8,11,12]

https://www.nature.com/articles/s41574-021-00553-7.pdf

Paracetamol



APAP = Paracetamol

"We recommend that APAP should be used by pregnant women cautiously at the lowest effective dose for the shortest possible time.
Long-term or high-dose use should be limited to indications as advised by a health professional."

https://www.nature.com/articles/s41574-021-00553-7.pdf

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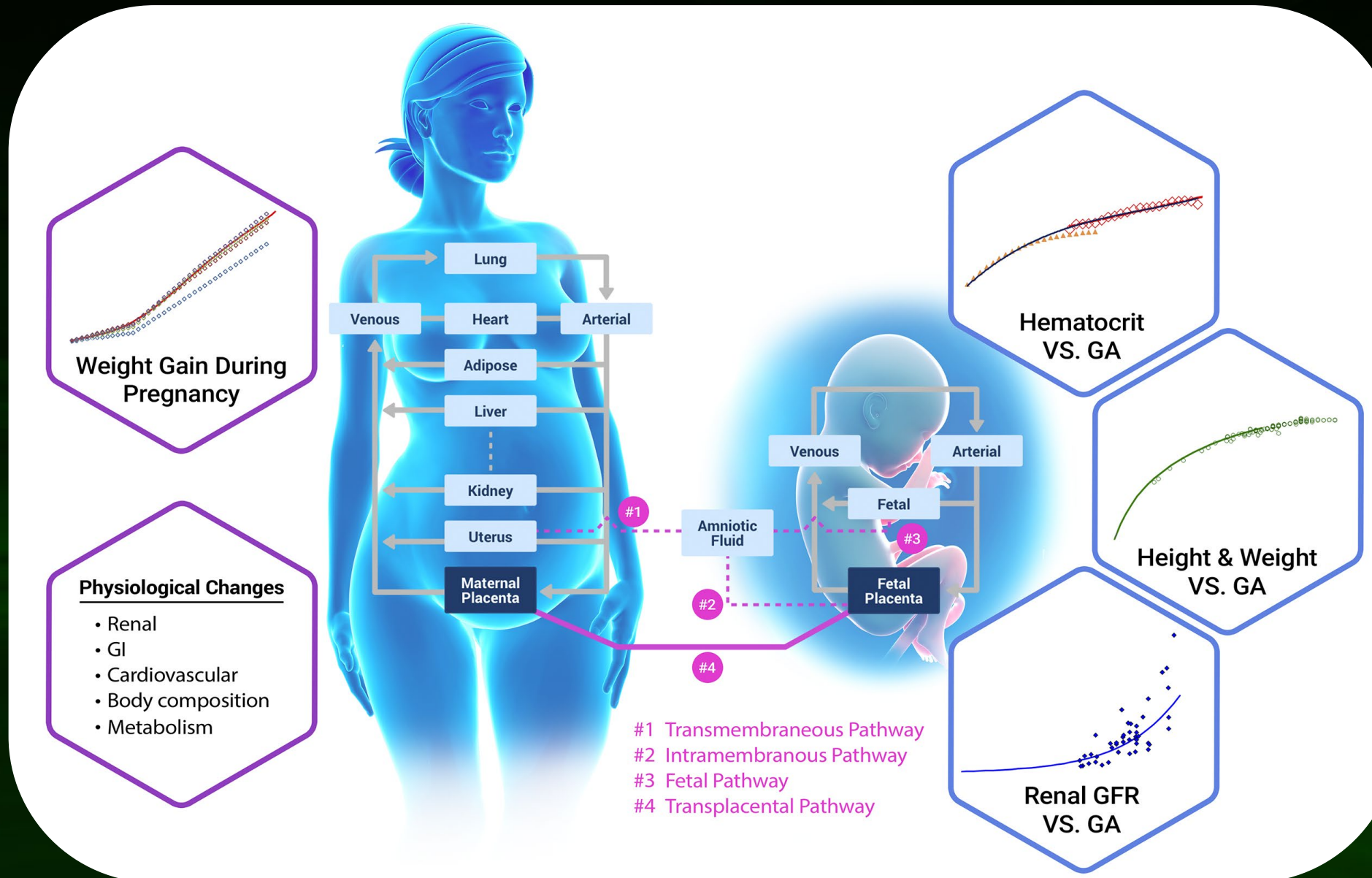
"For PK studies including pregnant patients, **physiological changes** during and after pregnancy **that are critical for drug absorption and disposition** may need to be considered in the model."

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-pregnancy-study-design-data-analysis-and-impact-dosing-and-labeling



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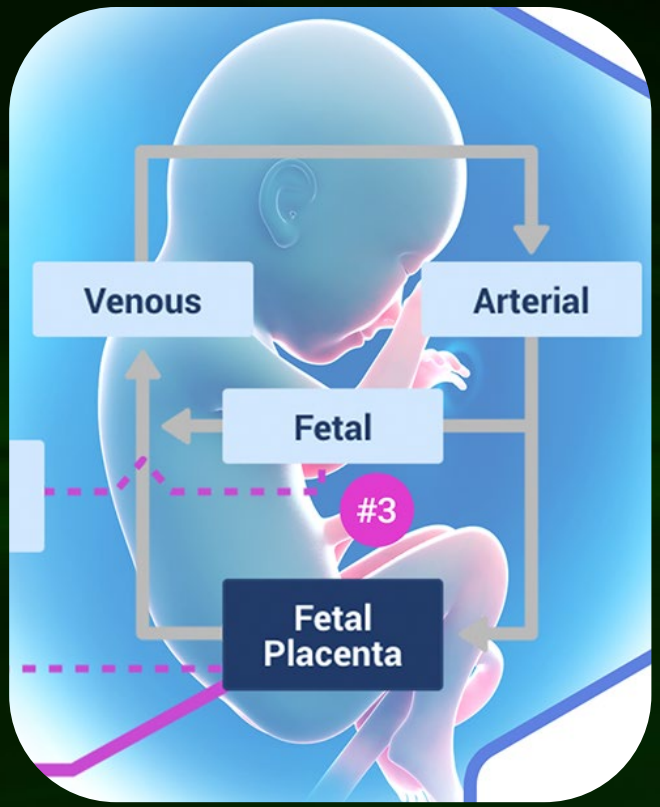
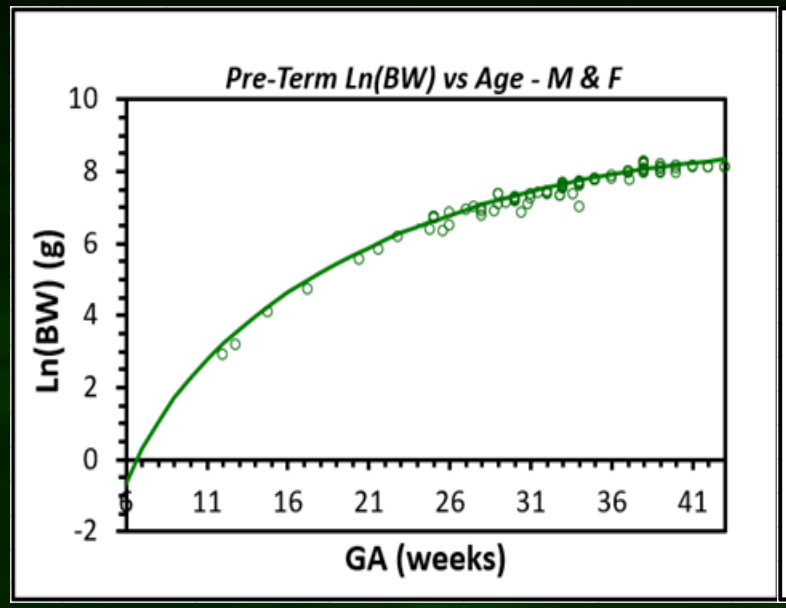
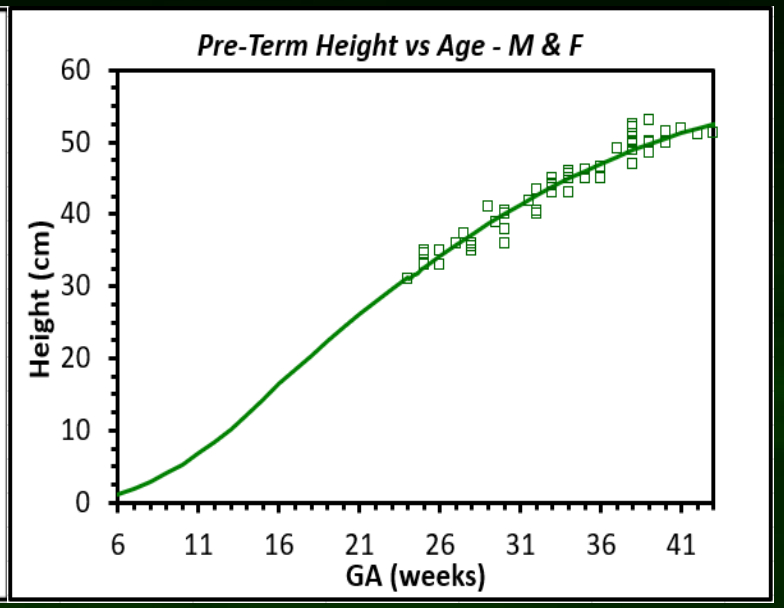
Fetal PBPK Model







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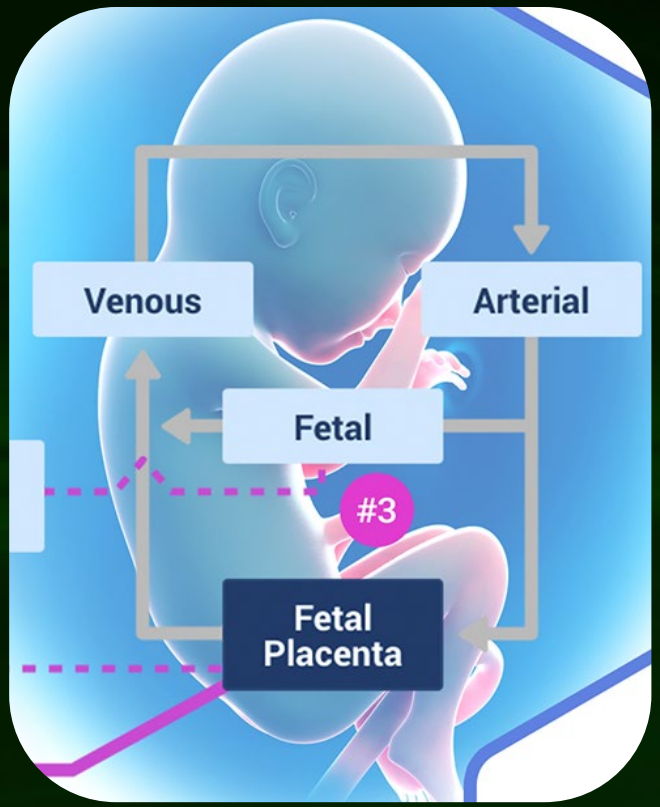
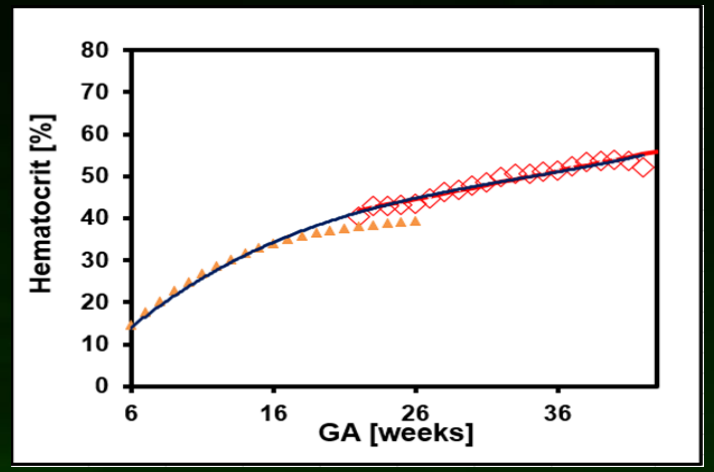
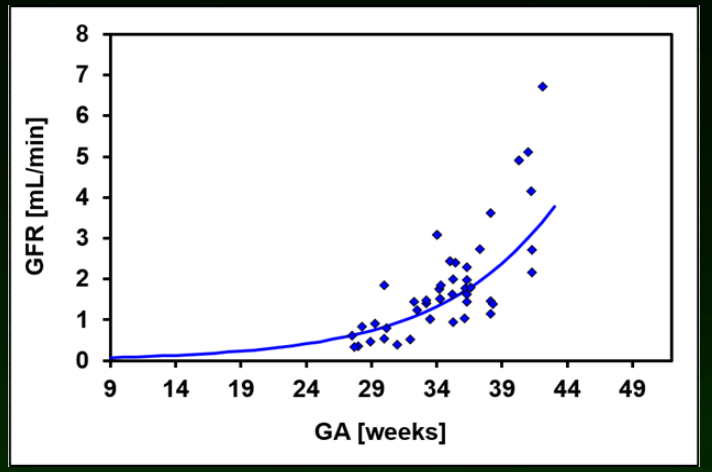
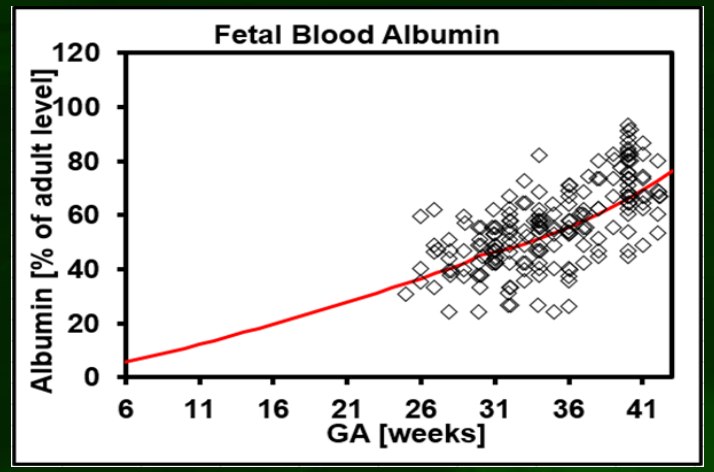
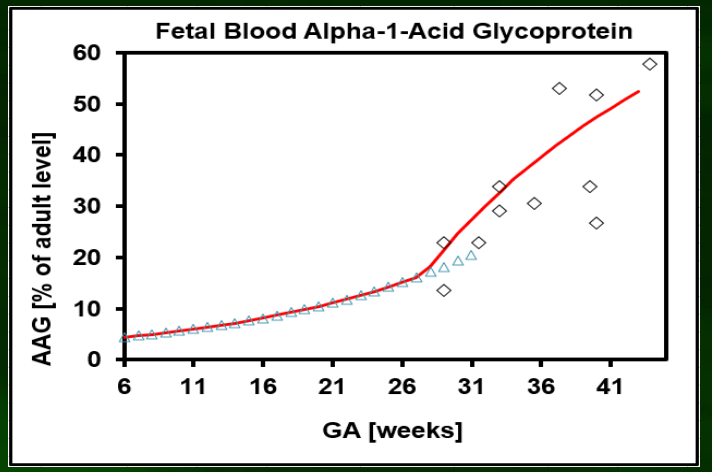
Fetal PBPK Model











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Maternal – Fetal Exchange

- Intramembranous pathway

rapid movement of water and solute that occurs between amniotic fluid and fetal blood within the placenta and membranes

➔ **Disappears after skin keratinization (GA 20)**

- Transmembraneous pathway

movement of water and solute between amniotic fluid and maternal blood within the wall of the uterus

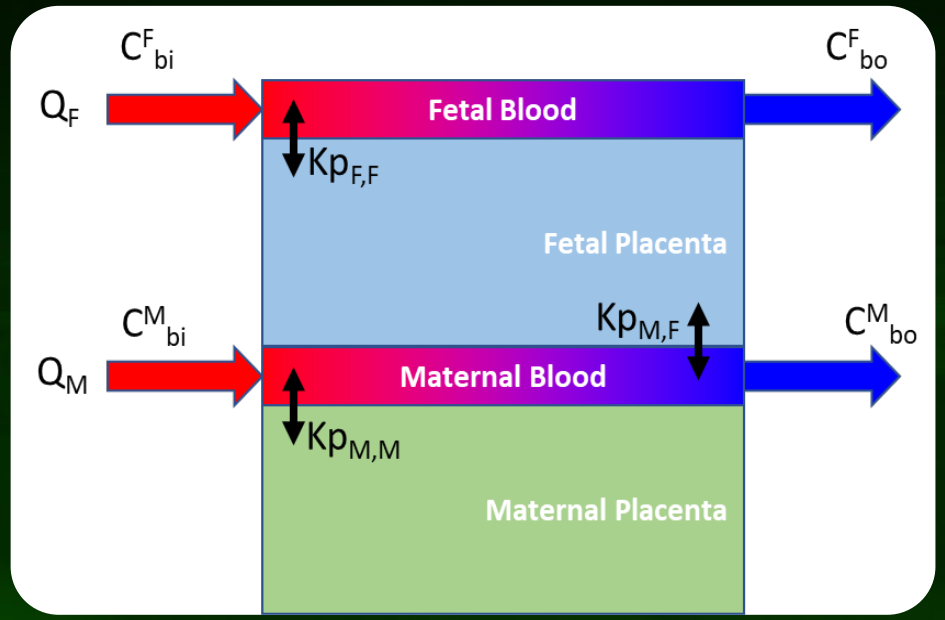
➔ Important in early gestation

- Fetal pathway

Movement of water and solute between amniotic fluid and fetal organs

➔ Starts between the 9th and 12th GA

- Transplacental pathway



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GastroPlus Demo

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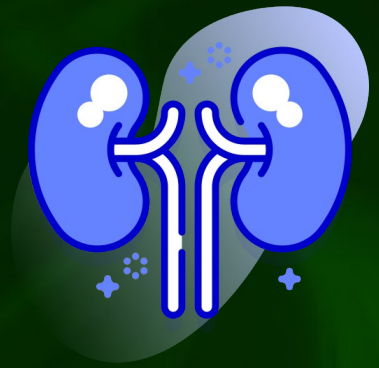
Case study 1

API eliminated solely by the kidney



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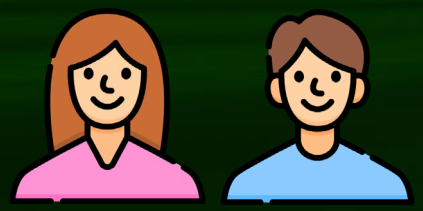
Cefuroxime

Model development and validation



Model adjustments Postpartum

Pregnancy prediction

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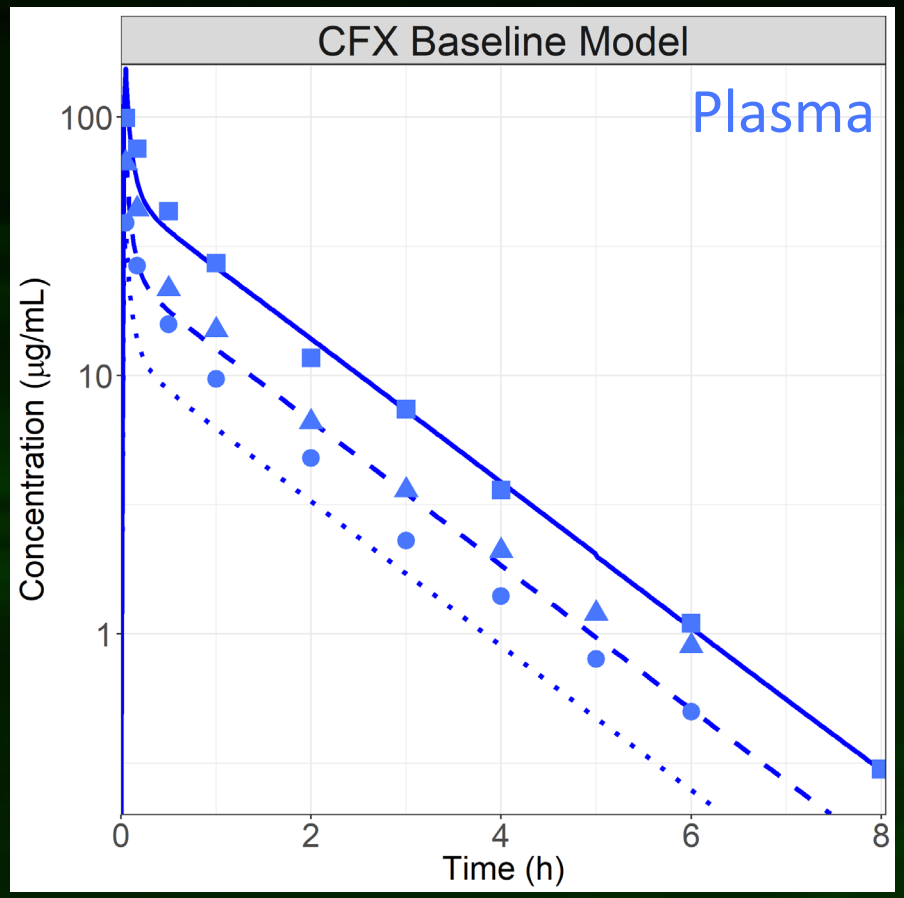
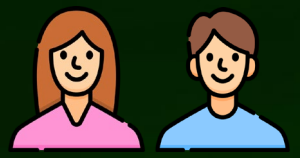
Cefuroxime



- CFX is cleared by renal filtration and active secretion
- All tissues defined as perfusion limited except the kidney
- Kidney secretion mediated by OAT3 and MRP4. Vmax parameters were fitted

➔ **PBPK model can reasonably described the observed concentration following IV administration at 3 doses**



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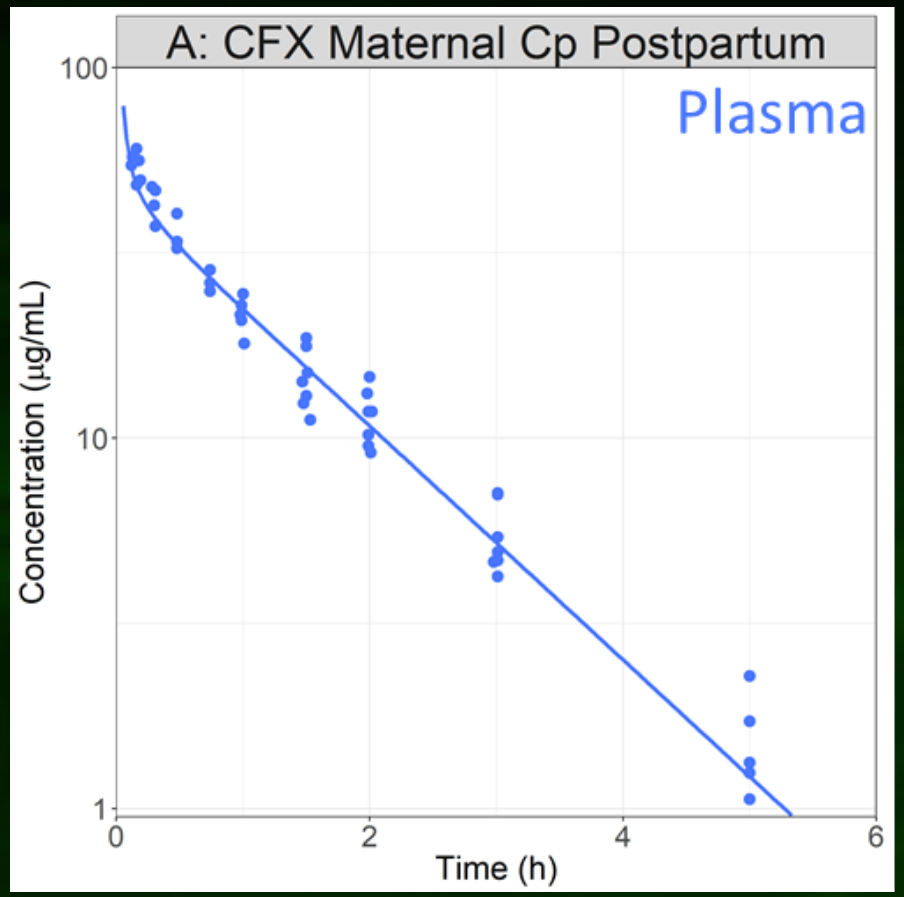
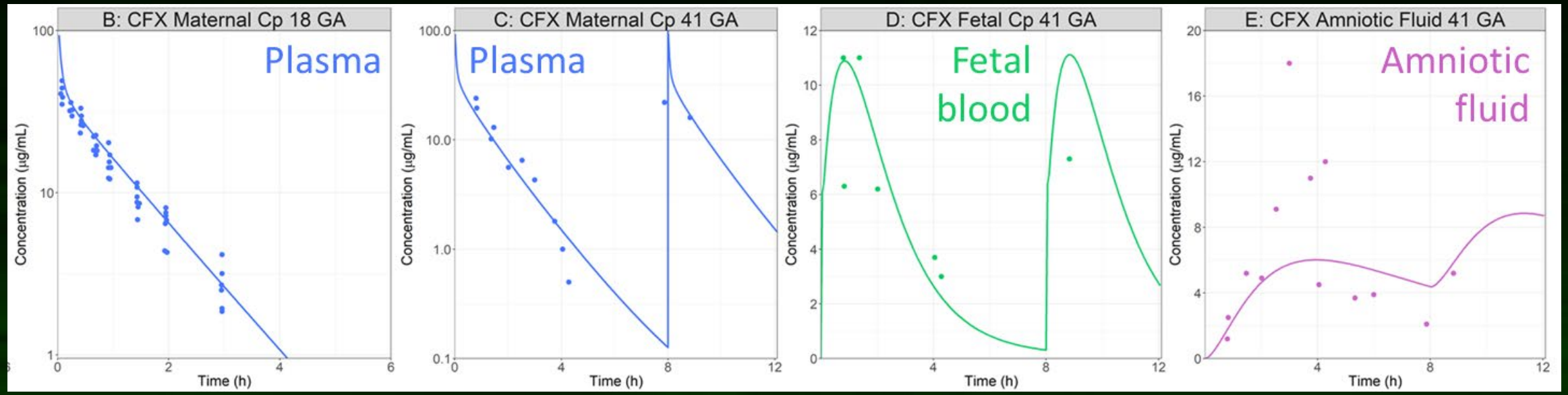
Cefuroxime



- Transporters Vmax parameters were adjusted to capture the urinary excretion data

➔ **PBPK model can reasonably described the observed concentration following IV administration in Postpartum subject**

Cefuroxime



- Placenta model was changed to permeability limited

➔ PBPK model can reasonably described the observed maternal and fetal concentrations following IV administration

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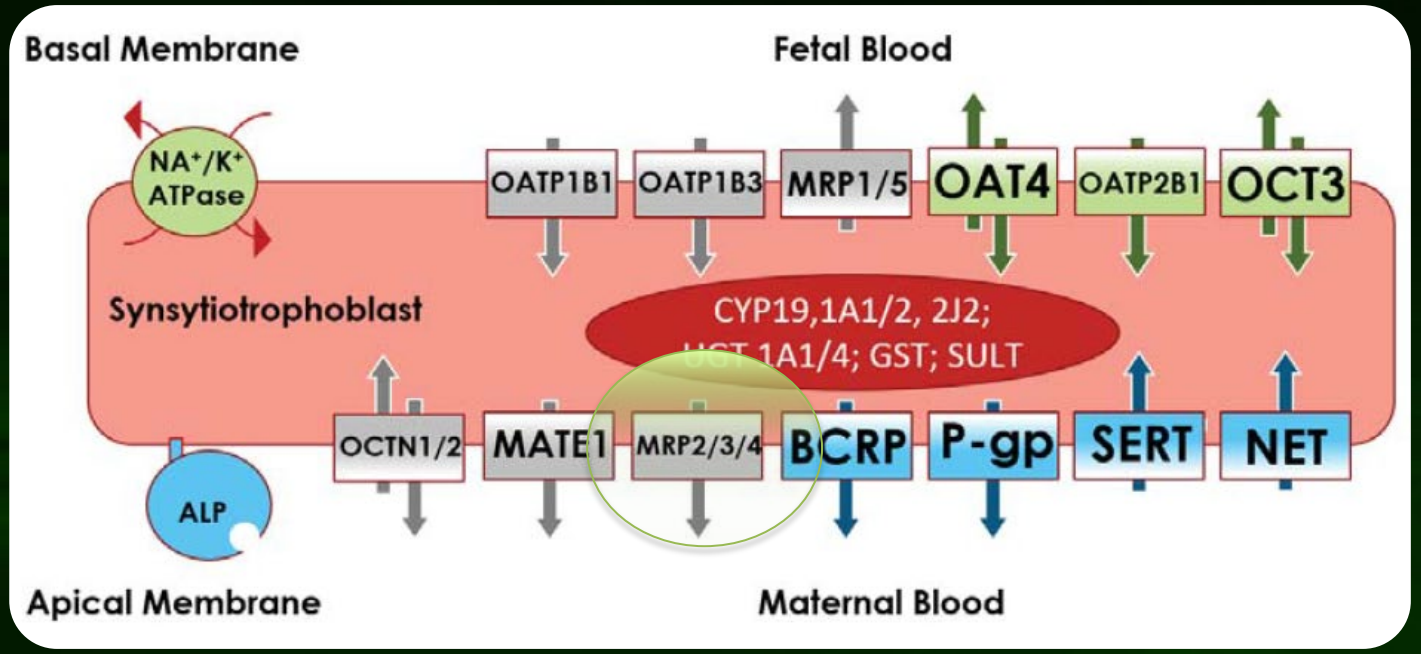
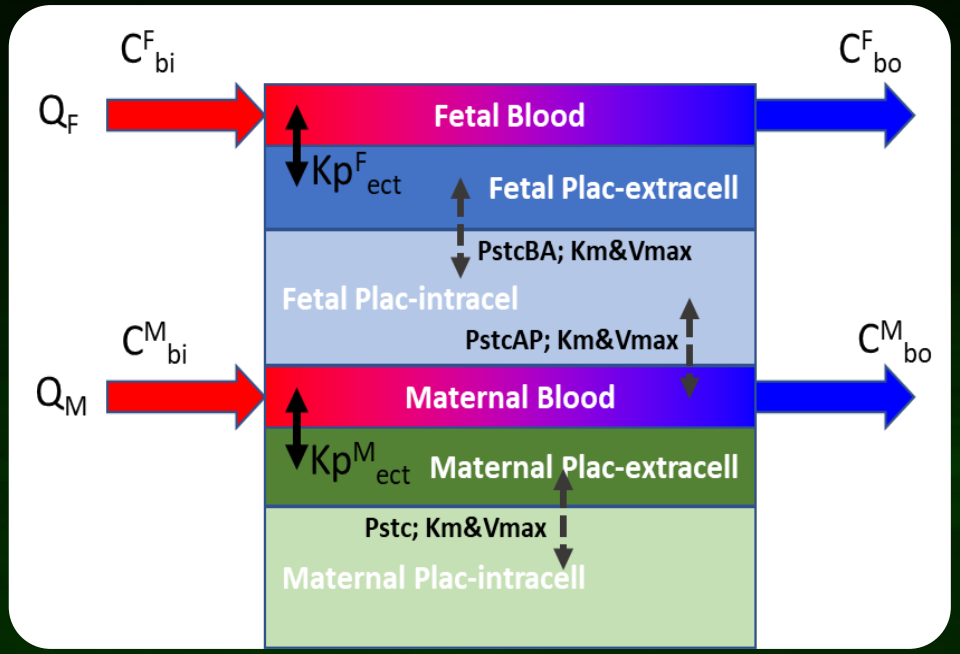
Cefuroxime





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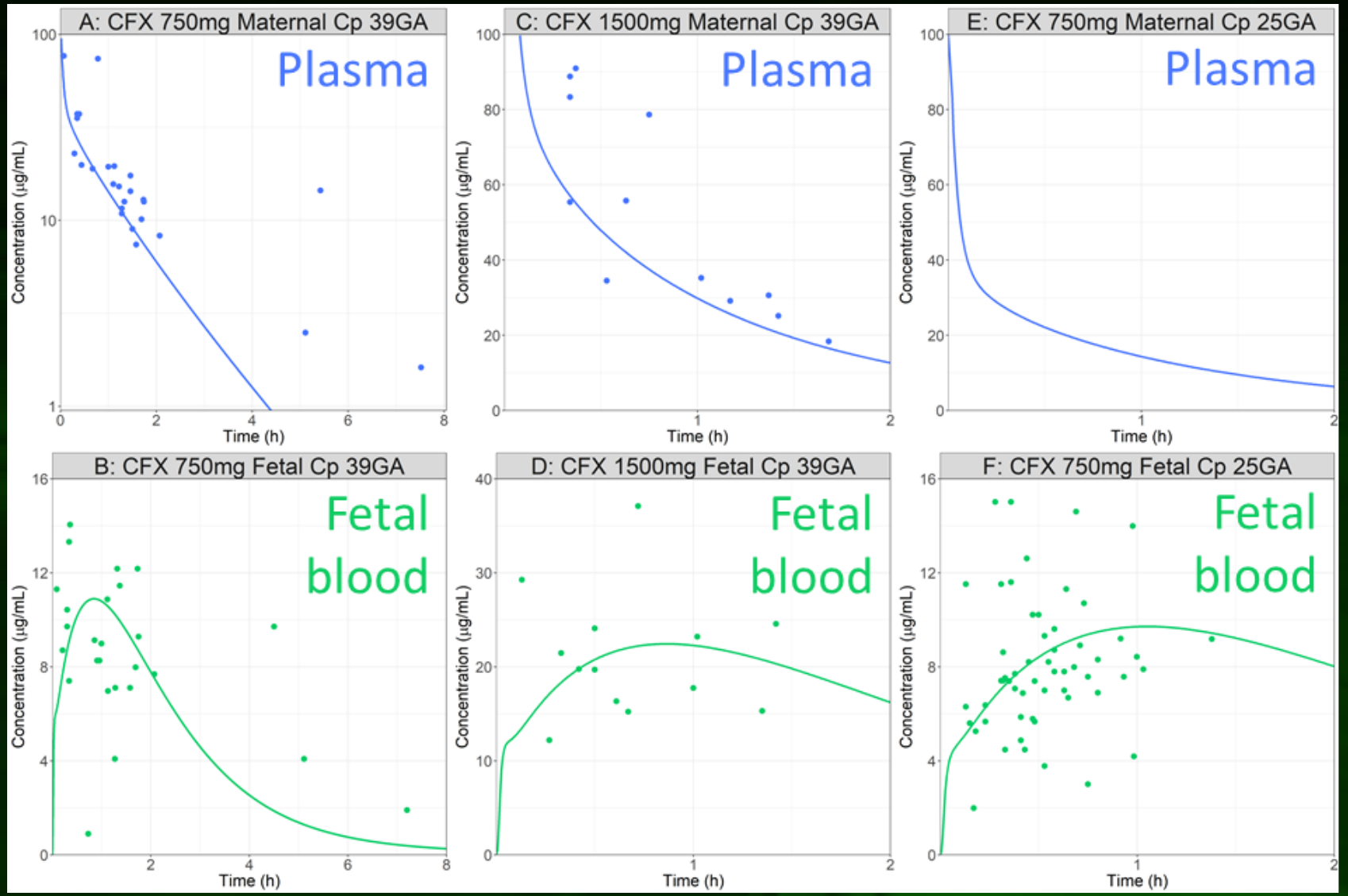
Cefuroxime


A: CFX 750mg Maternal Cp 39GA
Plasma
C: CFX 1500mg Maternal Cp 39GA
Plasma
E: CFX 750mg Maternal Cp 25GA
Plasma
B: CFX 750mg Fetal Cp 39GA
Fetal blood
D: CFX 1500mg Fetal Cp 39GA
Fetal blood
F: CFX 750mg Fetal Cp 25GA
Fetal blood
Concentration (µg/mL)
Time (h)

Case study 2

API eliminated solely by the liver

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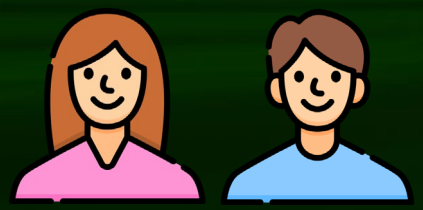
Metronidazole

Model development and validation



Model adjustments Postpartum

Pregnancy prediction

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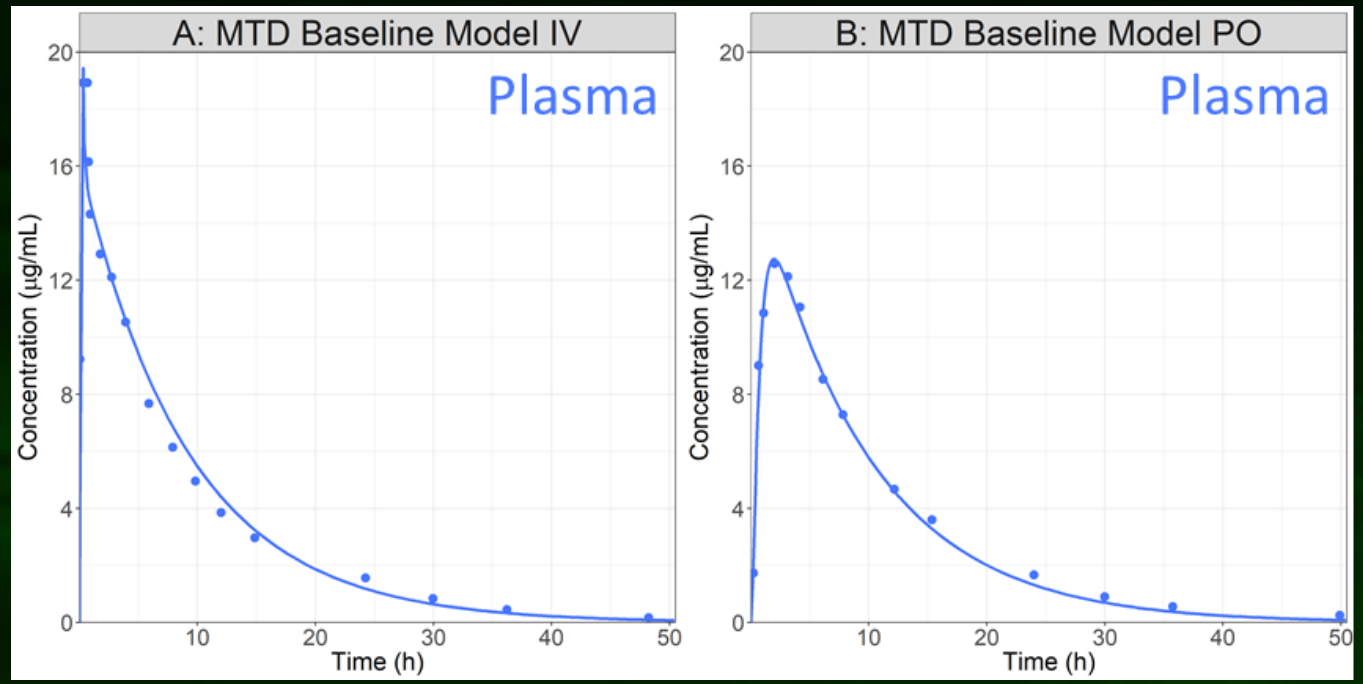
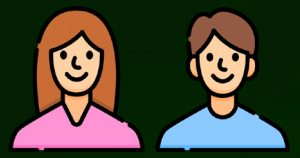
Metronidazole



- MTD is metabolized by the CYPs 3A4, 2A6, 2E1 and UGT
- All tissues defined as perfusion limited

➔PBPK model can reasonably described the observed concentration following IV/PO administrations.



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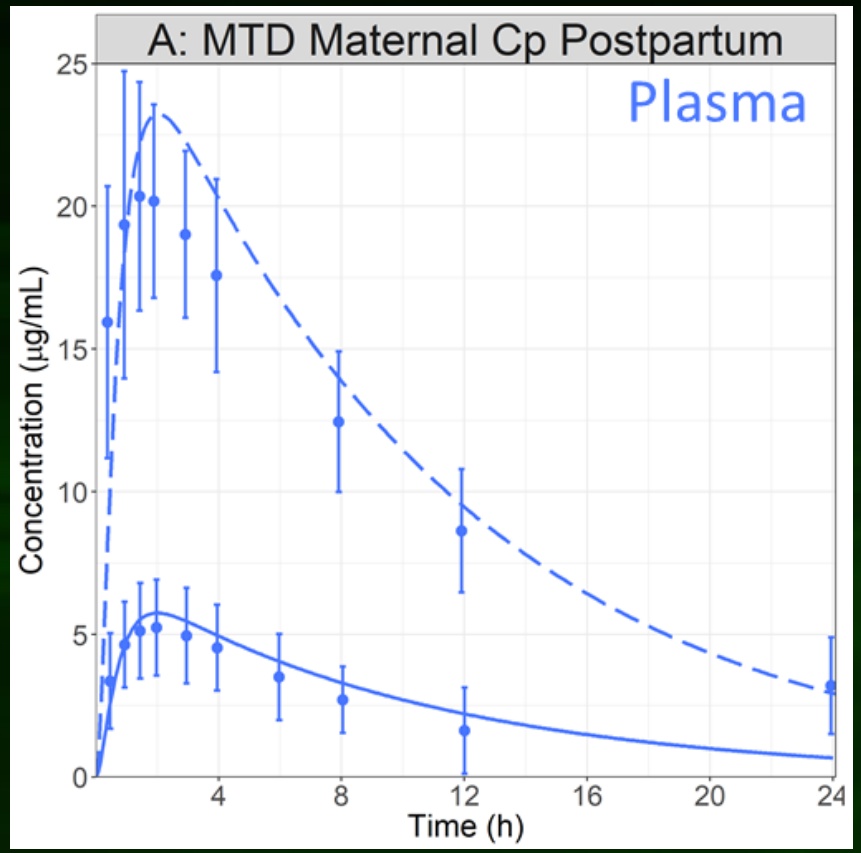
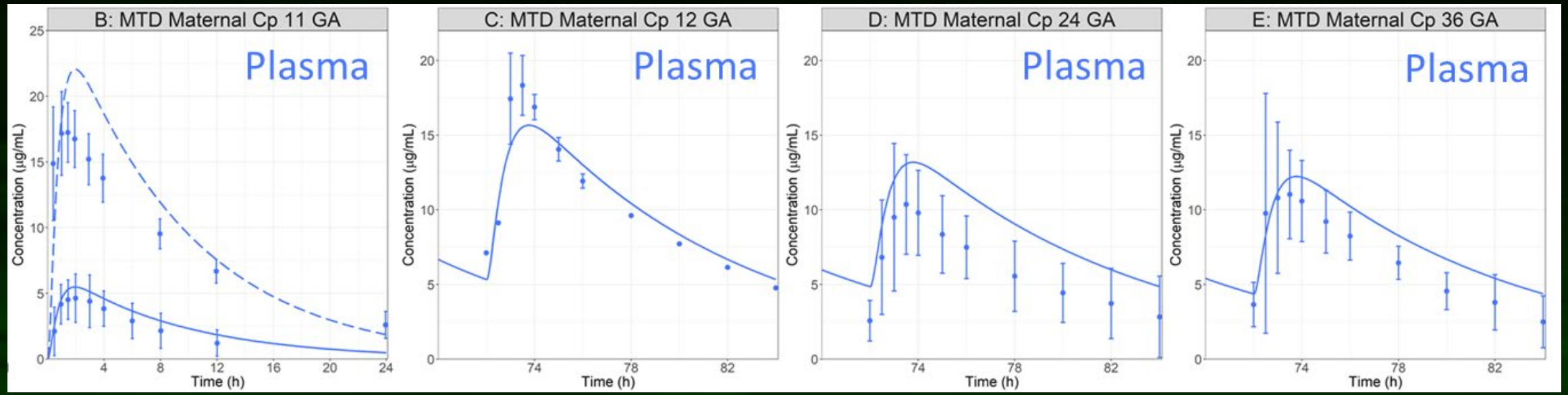
Metronidazole



- No model adjustment was made based on Postpartum data at 2 doses (0.25/1g PO)

➔ PBPK model can reasonably described the observed concentration following PO administration in Postpartum subject.

Metronidazole



➔ PBPK model can reasonably described the observed maternal Cp-time concentrations following PO administration at different stages of pregnancy

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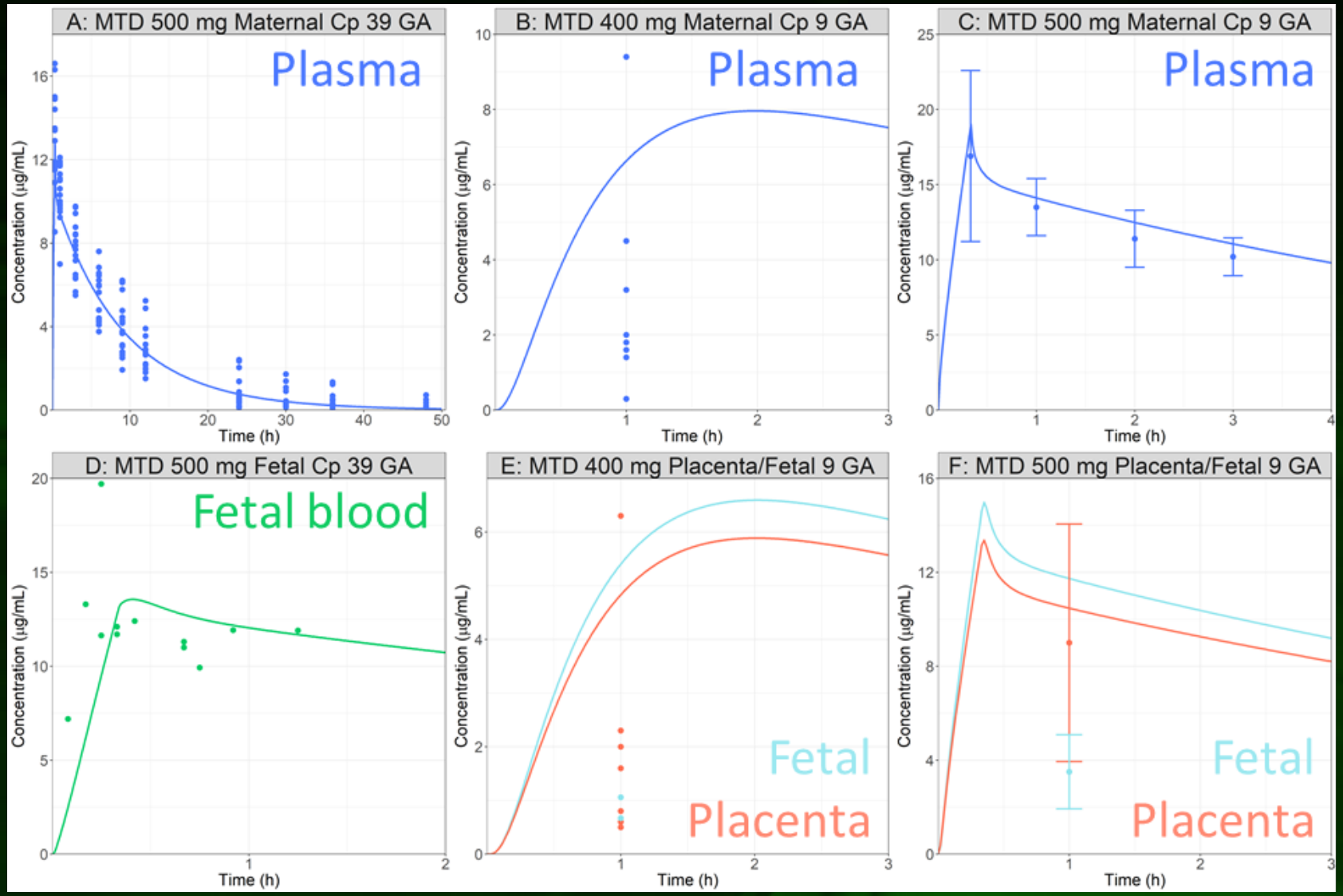
Metronidazole



Summary

- Ethics and safety concerns exist for Pregnant populations
- Pregnancy PBPK models can predict maternal and fetal PK/exposure
- Postpartum data may be interesting to calibrate the PBPK model
- Placenta model structure is probably dependent of the molecule of interest

To Learn More

The AAPS Journal (2021) 23:89
DOI: 10.1208/s12248-021-00603-y

Check for updates

Research Article

Theme: Celebrating Women in the Pharmaceutical Sciences
Guest Editors: Diane Burgess, Marilyn Morris and Meena Subramanyam

PBPK Modeling Approach to Predict the Behavior of Drugs Cleared by Kidney in Pregnant Subjects and Fetus

Ke Xu Szeto,[1] Maxime Le Merdy,[1] Benjamin Dupont,[2] Michael B. Bolger,[1] and Viera Lukacova[1,3]

Received 22 December 2020; accepted 27 April 2021

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- Dr. Haiying Zhou
- Dr. Viera Lukacova
- Dr. Michael B. Bolger

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Thank you and see you during the following workshops!

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