Modeling Motherhood I: Pregnancy PBPK in the Era of Personalized Medicine

10/08/2024 / André Dallmann

Conflicts of interest / disclaimer

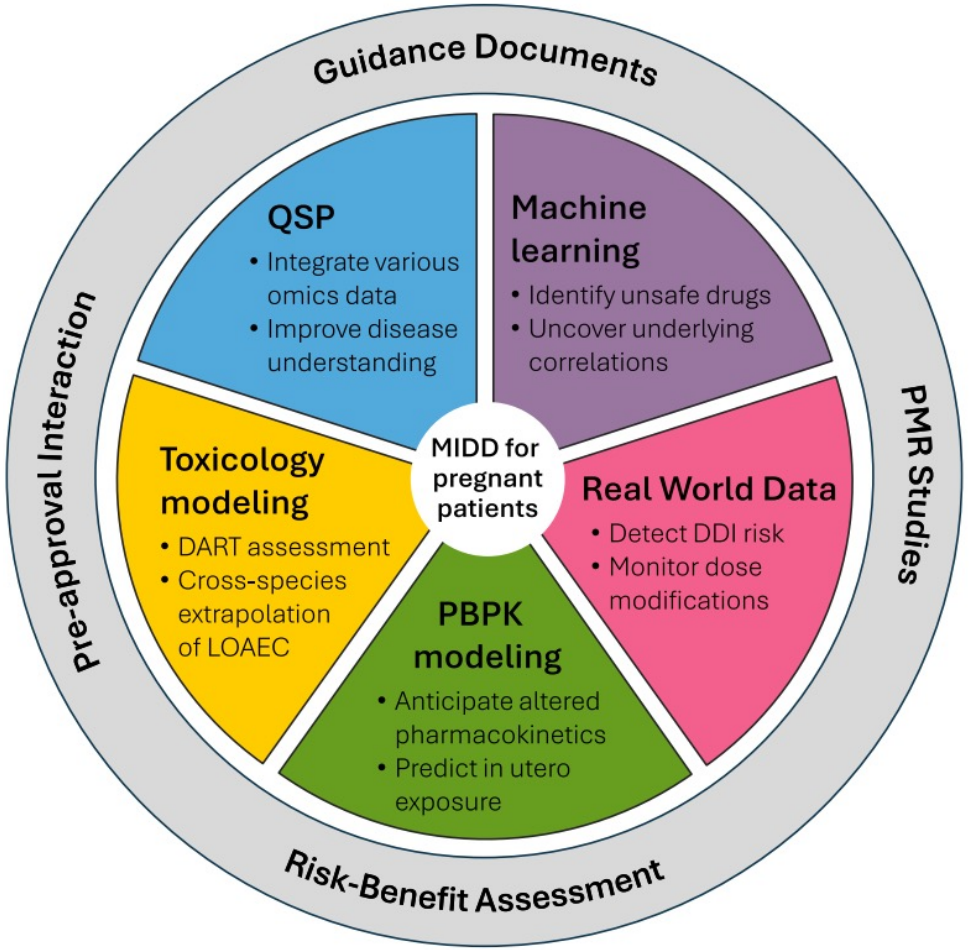
I am an employee of Bayer HealthCare SAS

I use Open Systems Pharmacology (OSP) software, tools, and models in my professional role

The views expressed in this presentation are my personal views

Rationale for applying pregnancy PBPK modeling

Enhancing pharmacotherapy in pregnant patients with MIDD: The promising role of PBPK Modeling



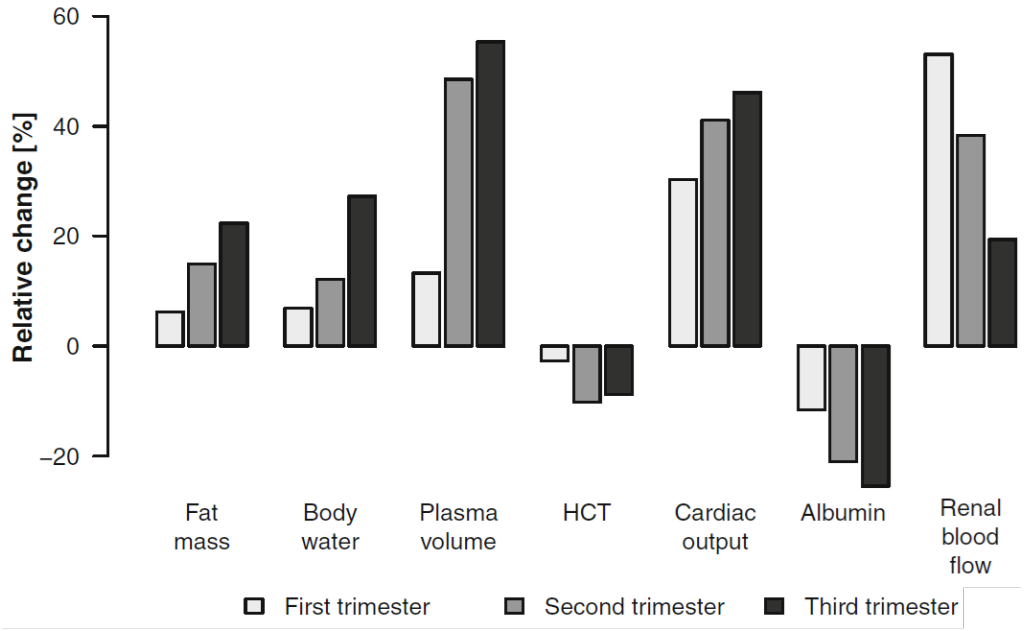
Dallmann A, et al. *CPT Pharmacometrics Syst Pharmacol*. 2024

Potential benefits of PBPK modeling for pregnancy:

- Research advancements through integration of existing data and prediction of outcomes in clinically untested or untestable scenarios
- Development of personalized dosing regimens for pregnant patients, accounting for relevant patient covariates
- Fetal and maternal exposure predictions can help identifying potential risks related to pharmacokinetics for both mother and fetus
- Computational M&S can represent an ethical alternative to conducting studies directly on pregnant people

Pregnancy-induced organ changes can significantly alter drug pharmacokinetics, potentially necessitating dosage adjustment

Physiological changes during pregnancy



Kazma JM, et al. *J Pharmacokinet Pharmacodyn.* 2020

US Label for Reyataz® Capsules (Atazanavir):

2.6 Dosage Adjustments in Pregnant Patients

Table 4 includes the recommended dosage of atazanavir capsules and ritonavir in treatment-naive and treatment-experienced pregnant patients. In these patients, atazanavir capsules must be administered with ritonavir. There are no dosage adjustments for postpartum patients (see Table 1 for the recommended atazanavir capsules dosage in adults) *[see Use in Specific Populations (8.1)]*.

Table 4 Recommended Dosage of Atazanavir Capsules and Ritonavir in Pregnant Patients[a]

	Atazanavir Once Daily Dosage	Ritonavir Once Daily Dosage
Treatment-Naive and Treatment-Experienced		
Recommended Regimen	300 mg	100 mg
Treatment-Experienced During the Second or Third Trimester When Coadministered with either H2RA or Tenofovir DF[b]		
In combination with either H2RA or tenofovir DF	400 mg	100 mg

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021567s026lbl.pdf

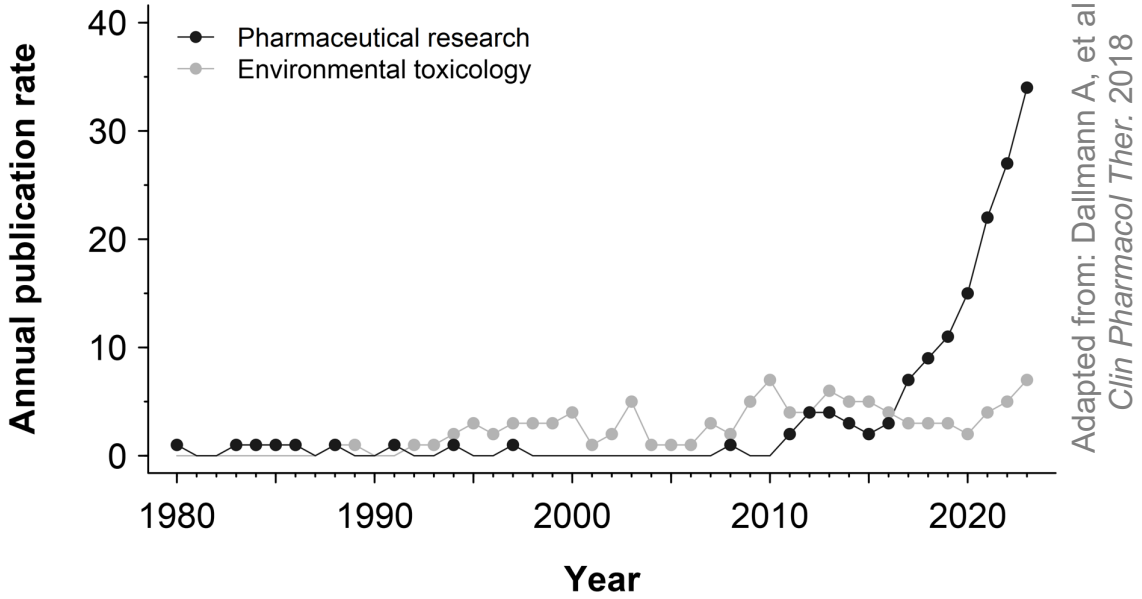
Rising trends: The surge in pregnancy PBPK modeling

// >250 articles on PBPK/PBTK modeling in animal or human pregnancy have been published

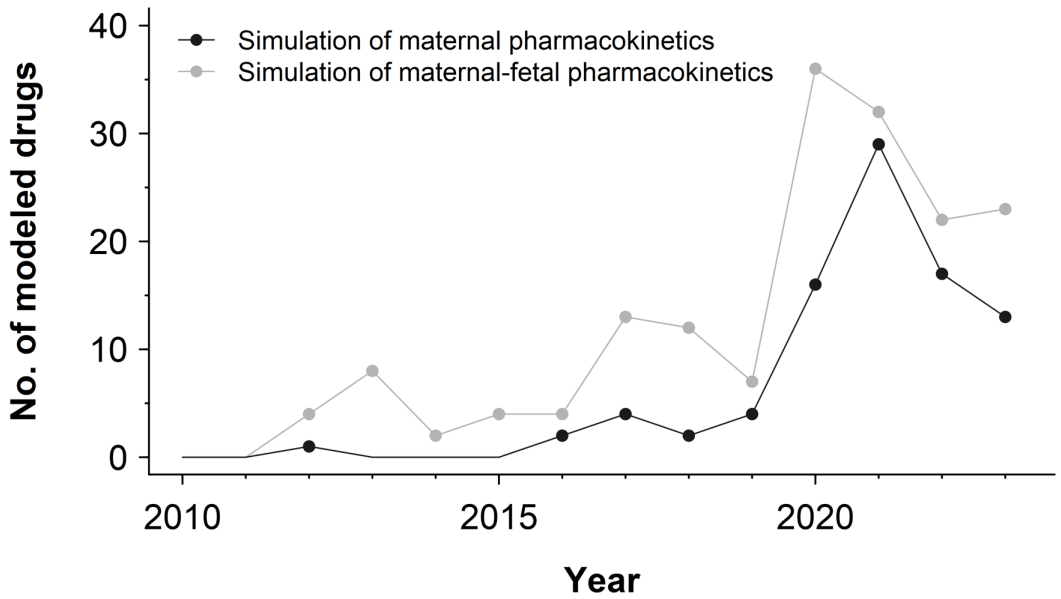
// Human pregnancy PBPK models have been developed for >80 chemically diverse drugs

// Pregnancy is the 3rd most frequently covered topic in OSP-based articles (Dallmann A, et al. *J Clin Pharmacol*. 2024)

Publication rate of articles on pregnancy PBPK/PBTK



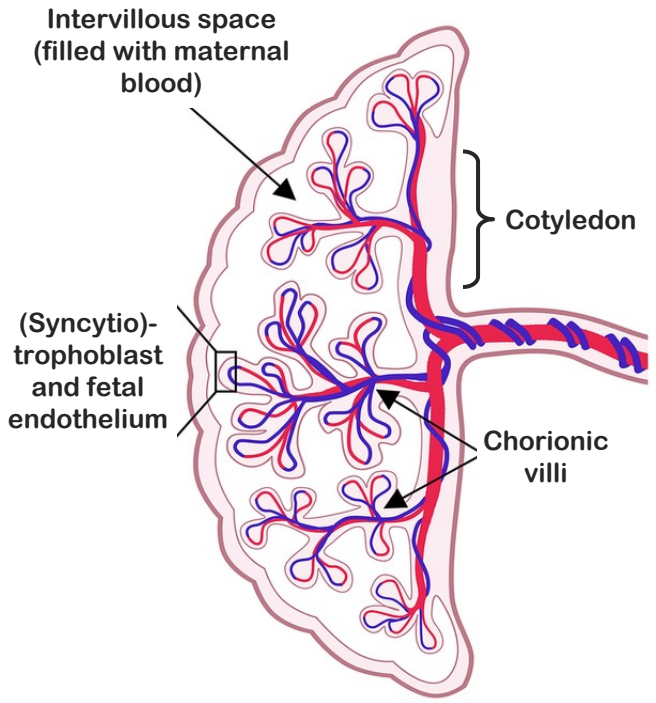
Publication rate of drugs modeled with PBPK



Simulating human placental drug transfer

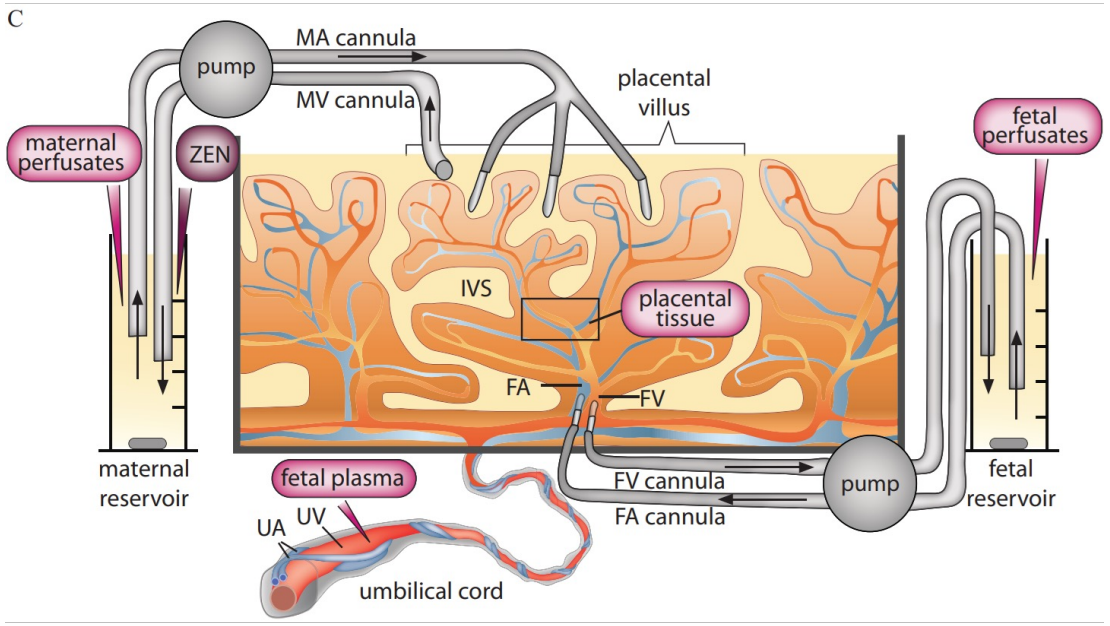
Understanding placental drug transfer in a micro-placental environment using the ex vivo cotyledon perfusion assay

Diagram of the placenta



Adapted from: Gaccioli F, et al. *Front Physiol*. 2016

Scheme with details of maternal and fetal side cannulation of an intact cotyledon



Warth B, et al. *Environ Health Perspect.* 2019

Cotyledon: Functional unit of the placenta where the maternal-fetal exchange of oxygen, nutrients, and other compounds takes places

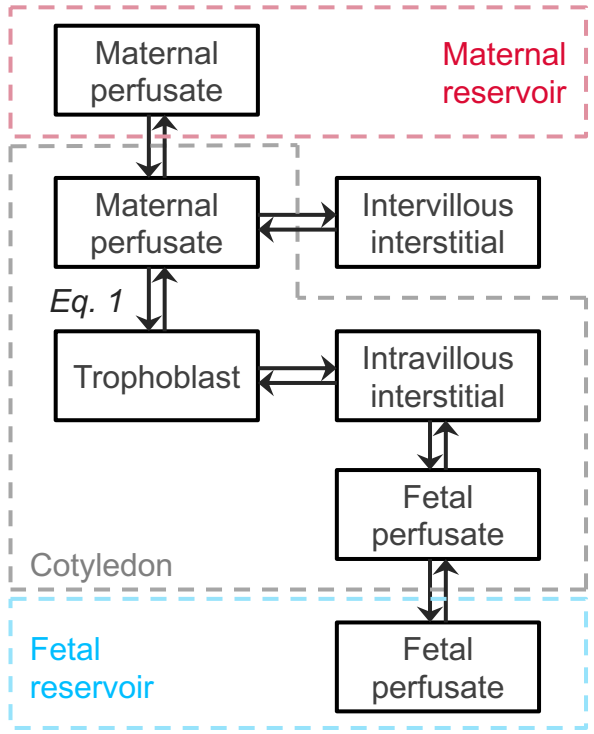
Open-source PBPK modeling approach to predict fetal exposure from ex vivo cotyledon perfusion kinetics

In silico replicate of the ex vivo cotyledon perfusion system in MoBi:

- **Open-access model:** All files are freely available in the pregnancy repository on OSP GitHub
- **Key parameters:** Placental transfer kinetics (Eq. 1) are predominantly influenced by D_{pl} and $K_{F:M}$:

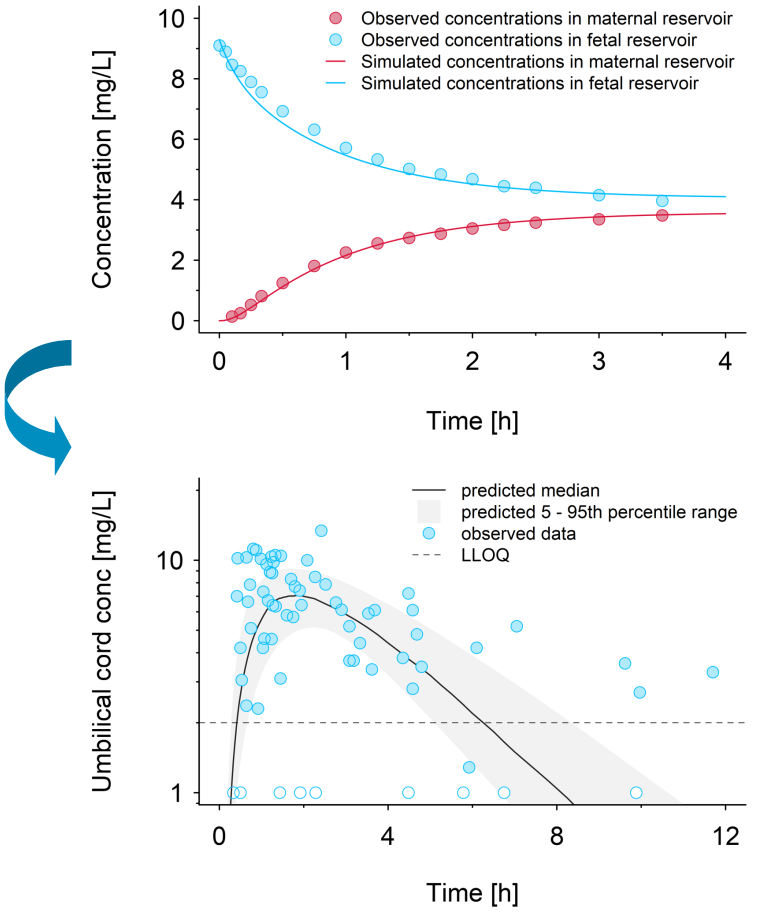
$$\frac{dN_{tblast}}{dt} = f_u \left(D_{pl} \times C_{perfusate} - \frac{C_{tblast}}{K_{F:M}} \right)$$

- **Parameter Optimization:** D_{pl} and $K_{F:M}$ are often unknown, but can be fitted to measured kinetic data
- **Predictive integration:** Integrating D_{pl} and $K_{F:M}$ in whole-body PBPK models enables pharmacokinetic predictions in humans



Mian P, et al. *Front Pediatr.* 2021

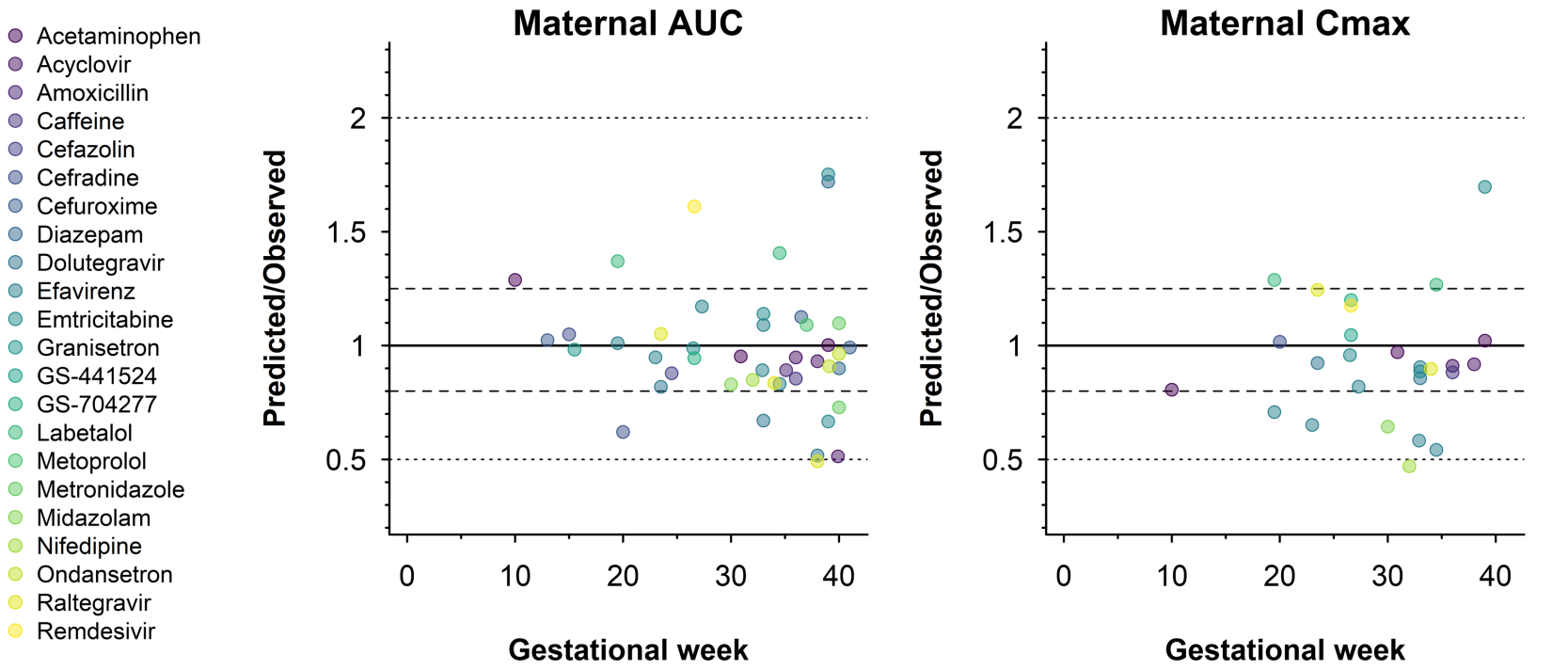
Example: Acetaminophen (paracetamol)



Mian P, et al. *Front Pediatr.* 2021

Outlook

OSP PBPK models show good performance for predicting maternal pharmacokinetic changes



All values (*n*)	45	27
Within BE range [%]	71%	85%
Within 2-fold error range [%]	98%	96%

→ Fetal exposure modeling requires further efforts: additional clinical data and fetal models are needed

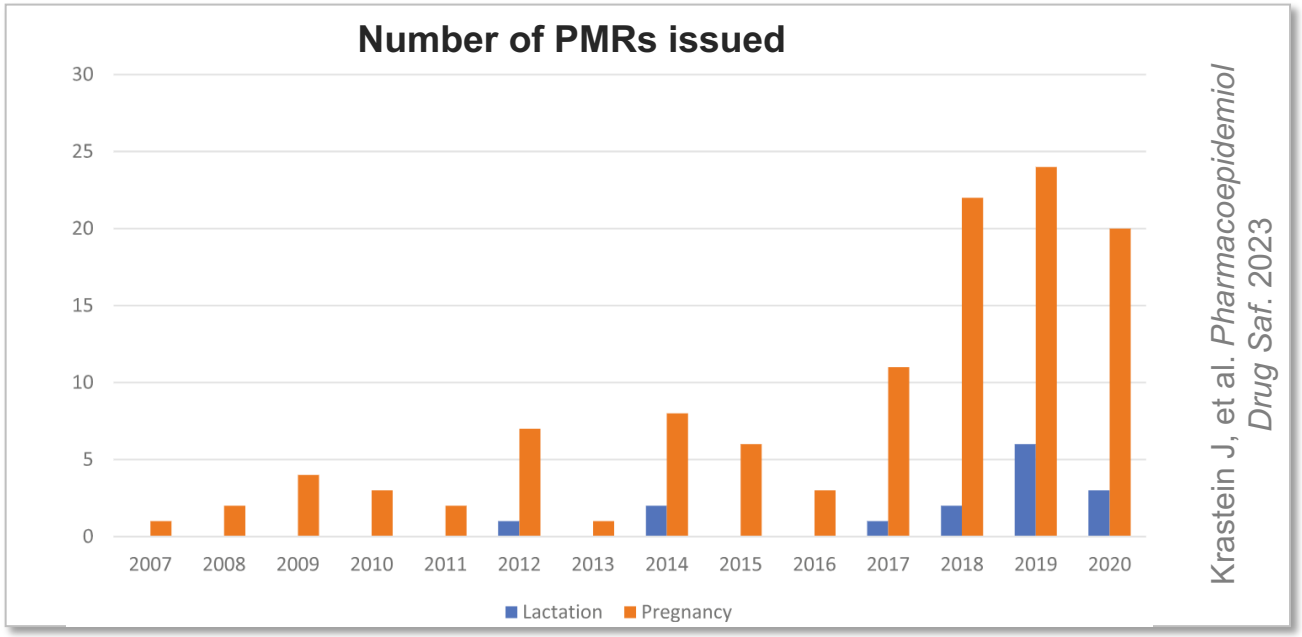
Regulatory interactions regarding pregnancy PBPK modeling are currently limited

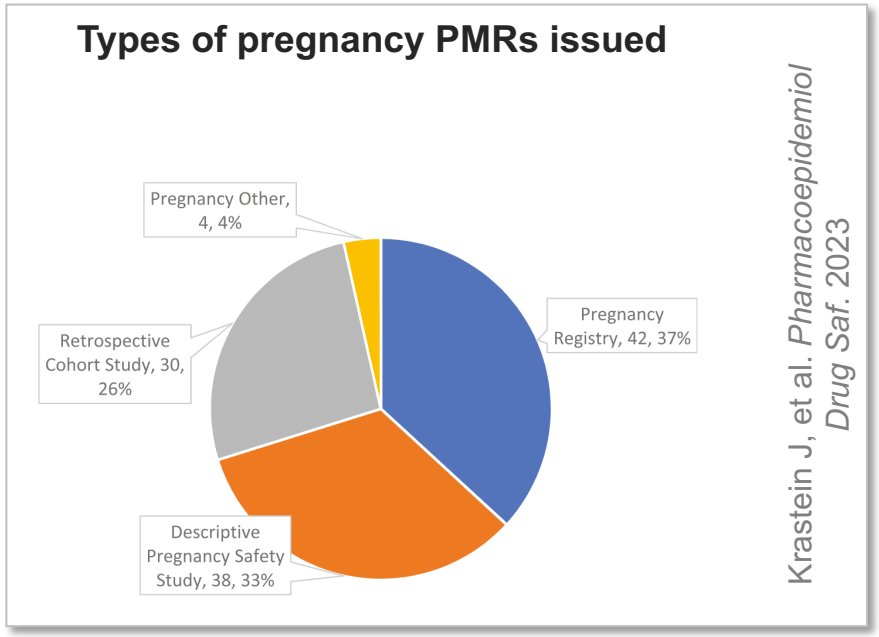
- Currently, there are no documented examples of pregnancy PBPK models applied to drug labeling
- **FDA** encourages – under certain circumstances – the use of modeling & simulation to assess whether dosage adjustment is needed in pregnant people (*Guidance for Industry: Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*)
- **MHRA** is collaborating with the **Bill and Melinda Gates Foundation** to evaluate existing PBPK models to inform dosing in pregnant people in the UK:
  - Preliminary results have been presented for pregnancy PBPK models for renally excreted drugs developed in GastroPlus, Simcyp, and OSP.
  - **MHRA's conclusion:**

> "Changes in passive renal processes during pregnancy are reasonably well captured by the PBPK models and similar results were obtained with all softwares that is, SIMCYP, Gastroplus, and PKSim."
>
> Coppola P, et al. *J Clin Pharmacol.* 2020

Issuance of PMR studies might enhance the applicability of pregnancy PBPK modeling in drug development

- At the time of marketing approval, there is generally **little to no information** on drug safety and efficacy when used during pregnancy
- The US regulatory agency (FDA) increasingly issues post-marketing required (**PMR**) studies
- Maternal-fetal PBPK modeling is rarely used in drug development, but it might potentially reduce the need for PMR studies → **Pregnancy PBPK holds largely untapped promise in this domain**





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Thank you!

Bye-Bye