Session 2: Modeling Pregnancy Pharmacokinetics

Industry perspective on role of PBPK modeling in pregnancy

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Sr. Directors
Certara

The need?

UNIVERSITY OF BIRMINGHAM

Birmingham Health Partners
Collaboration. Innovation. Application.

Healthy Mum, Healthy Baby, Healthy Future

The Case for UK Leadership in the Development of Safe, Effective and Accessible Medicines for Use in Pregnancy

May 2022

6. Increasing investment in pregnancy research

Reproduction and childbirth is a 'Cinderella' area of research. It receives neither the funding, attention, nor status that other areas of science and health research garner. Though this area directly affects up to 51% of the population – in truth the entire population, since we are all a product of reproduction – only 2.1% of health research funding in the UK is spent on reproductive health and childbirth.

The UK spends about £51 million a year on pregnancy research, a small fraction of which is relevant to medicines use in pregnancy. For every £1 spent on pregnancy care in the NHS, only 1p is spent on research. For comparison, pregnancy-related litigation costs to the NHS in 2018-19 were £2.5 billion, making up approximately 49% of the total cost of clinical negligence claims.

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making up approximately 49% of the total cost of clinical negligence claims.

This paucity of investment – and subsequent paucity of pregnancy R&D – has serious knock-on effects. One witness noted that the UK remains 'at a 1990s level for progress in this field', where other areas of health science have flourished. This deficit runs through every stage from basic biology to pre-clinical medicines screening, and translation into novel therapies and other interventions which could save lives and relieve suffering for many mothers and babies.

Despite remarkable scientific advances in our understanding of human health and disease in other areas, we know little in comparison about basic human reproductive biology – the early embryo; how medicines affect the workings of the placenta; how medicines cross the placenta from mother to child; the handling of medicines by the fetus; and much of the basic physiology of pregnancy is still poorly understood. Improved understanding of discovery science in reproductive health and embryology is vital. Many of the issues in pregnancy are laid down at the earliest stages – in the first 12 weeks of gestation - so knowing the science of this early stage may be particularly crucial.

Understanding these basics better would help at an earlier stage in the process of designing and developing medicines for use in pregnancy. For example, if researchers could show that a new medicine does not cross the placenta at all, this would provide some reassurance for testing that specific drug in clinical trials with pregnant women.

Better pre-clinical tests would lead to a more secure and safe knowledge base before medicines go into clinical trials with pregnant women. This would mean potentially, that medicines likely to be harmful in pregnancy, would be screened out early. Good *in vitro*, *in vivo* and *in silico* models are needed to screen drug candidates and test the potential effects of medicines given in pregnancy, before the human clinical trial stage.

However, our lack of basic research knowledge and the unique nature of human pregnancy have been barriers.

There are no good animal models to test medicine candidates in pregnancy. Those commonly used have very different placental systems from humans, and do not naturally develop the pregnancy complication pre-eclampsia, for example.

Recent advances bring some hope to the field. A human placental stem cell line was successfully developed by Japanese researchers in 2018. And technological improvements in areas such as 'virtual' clinical studies, better computer modelling, microfluidics and organoids (bioengineered mini organs in the lab) means that we may see effective 'placenta-on-a-chip' models in the next three to five years. The UK could pioneer these technologies, and in turn accelerate pregnancy medicines research faster - provided research investment was prioritised.

The Commission also heard from different sectors that the low status and funding of reproductive science creates difficulties in attracting and retaining researchers. Too often, young scientists are lost to higher-profile and better-resourced areas such as cancer. This is also a challenge on the clinical side of research and care – there are fewer than 10 obstetric physicians in the entire UK, mostly based in London and Oxford.

Together, the Commission was convinced of the need for a clear national strategy related to pregnancy research, to address funding issues across the field: from discovery and translational science to clinical trials and evaluations; and to make the sector more attractive to recruit and retain talented researchers. There was also a compelling rationale to develop better and more efficient pre-clinical screening tools and reproductive toxicology models. Providing clear focal points of public and private investment as 'hubs' for a coherent UK community, well-linked with wider global funders and innovators, will be crucial to accelerating progress.

'We basically do not understand enough about the physiology of normal pregnancy and certainly about pregnancy complications, in order to know what we should be targeting.'

Professor Graham Burton, University of Cambridge

RECOMMENDATIONS

1. **Deliver effective advocacy for medicines in pregnancy** through a coalition of pregnancy and baby charities, working together with the public, researchers from academia and industry as well as Government to create a shared vision for safe medicines evaluation and development in pregnancy. This will allow for clear and consistent messages to the public and clinicians.

2. **Pregnant women should be offered the opportunity to take part in all clinical trials of medicines that could be used in pregnancy,** unless there are specific safety concerns.

3. **Prioritise updates for existing medicines with the potential to be used in pregnancy,** with regulators and industry working towards pregnancy-specific information on safety, dosing and effectiveness. Resources should be put in place to maintain this activity, particularly for generic medicines.

4. **De-risk insurance processes** for early and late phase clinical trials of new and existing medicines for use in pregnancy, using lessons and successes from other challenges.

5. **Incentivise industry to develop pregnancy-specific medicines,** utilising cross-stakeholder working to ensure that the UK is in a globally-competitive – and globally-collaborative – position to drive drug development for pregnancy-specific conditions.

6. **Establish a UK-wide national network of research centres** encouraging major public and private investment and collaboration in pregnancy research expertise and infrastructure. This will ensure sustainable drug development from discovery science through to pre-clinical screening tools and clinical evaluation.

7. **Improve use of routine clinical care maternity data** to help assess the safety and effectiveness of new and existing medicines used in pregnancy. Establish a designated maternity 'Health Data Research Hub' through Health Data Research UK with a focus on medicines evaluation in pregnancy.

8. **Appoint a UK Steering Committee** aligned to the Government's Women's Health Strategy to deliver the above recommendations, with oversight of implementation, ensuring milestones are set and monitored.

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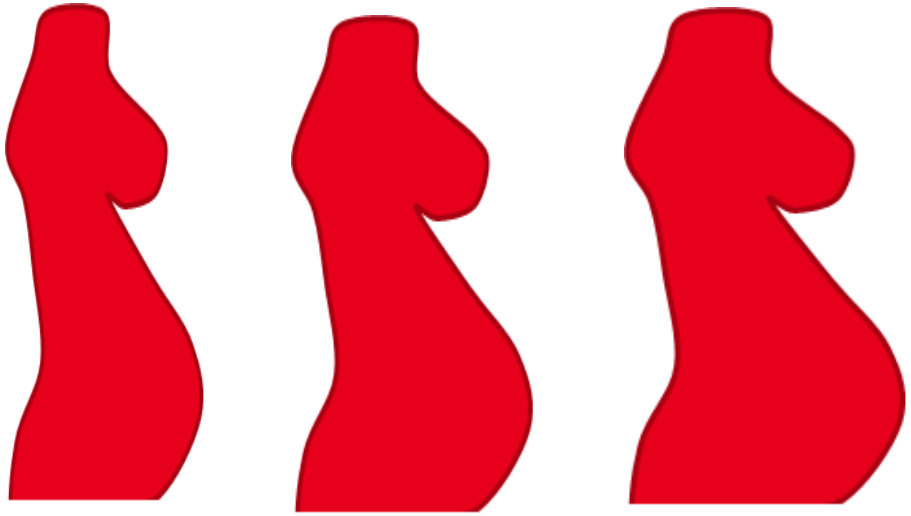
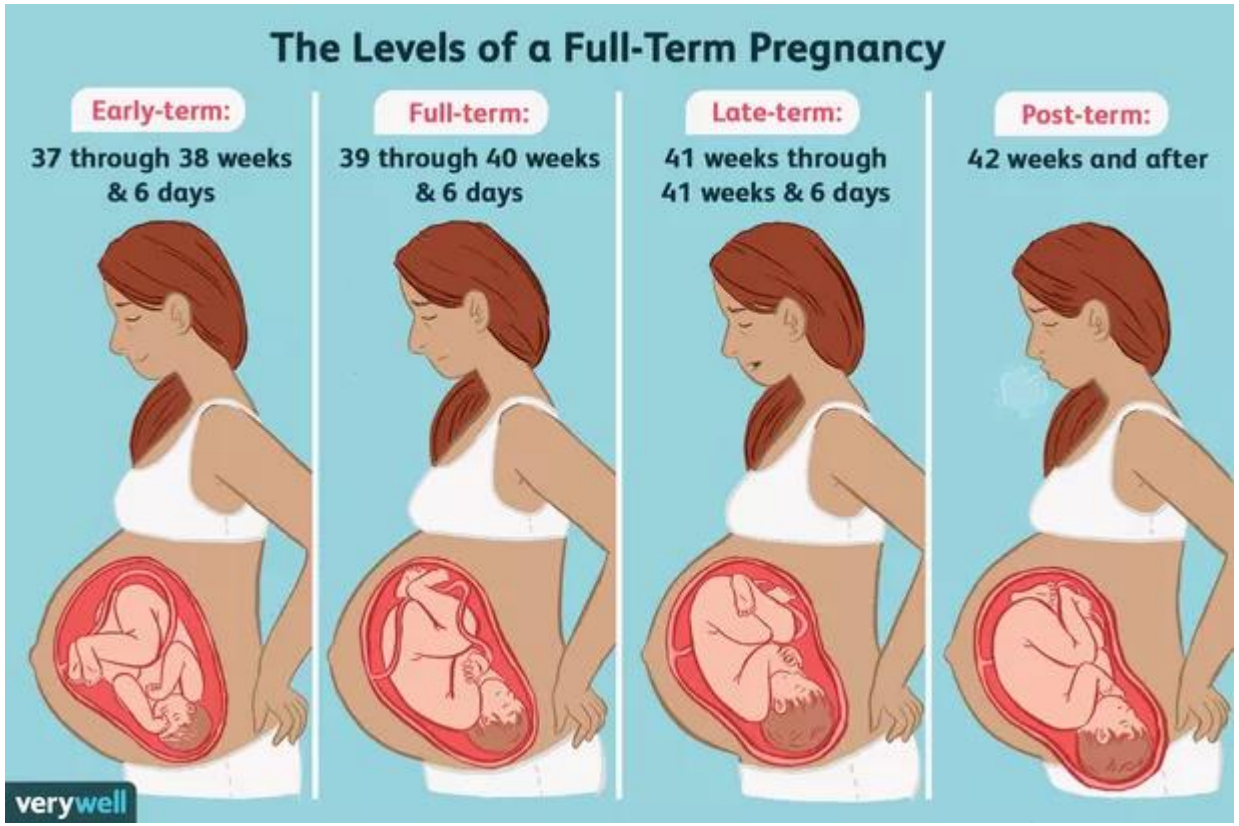
Gestational stage and terms of pregnancy (consider both pregnant and unborn)

The gestational stage as defined per U.S. Department of Health and Human Services (HHS) recommendations:

- 1-12 weeks for the 1st trimester,
- 13-28 weeks for the 2nd trimester
- 29-40 weeks for the 3rd trimester



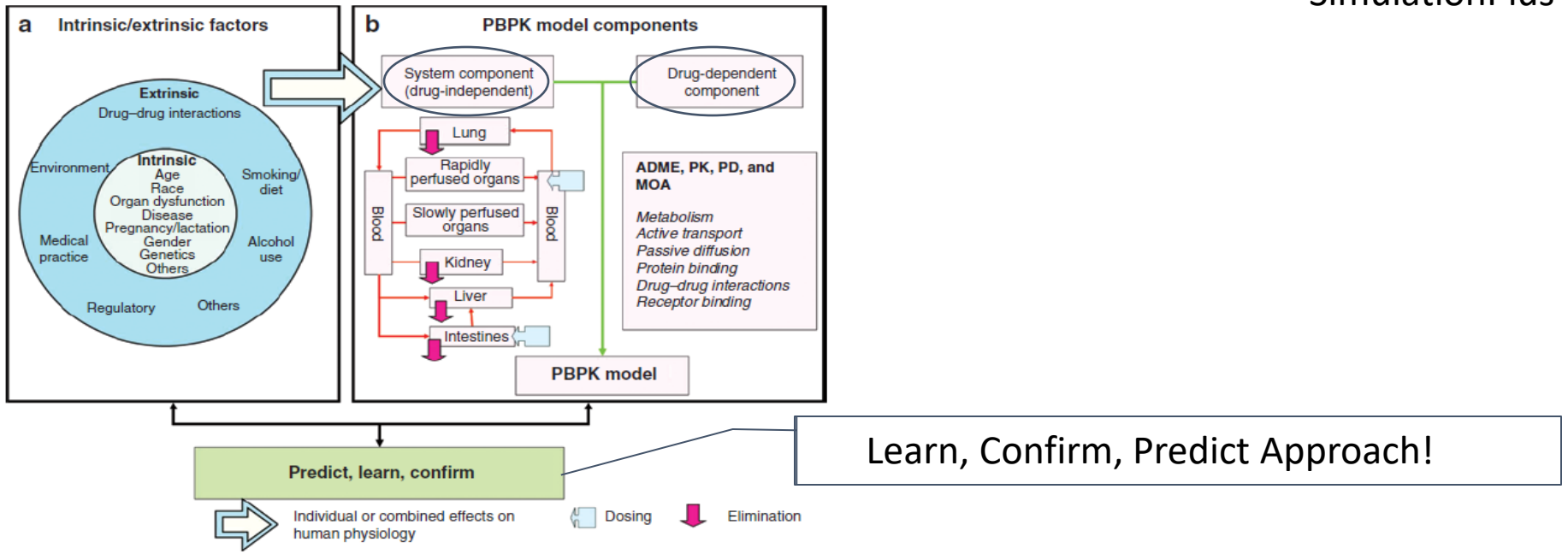


https://www.womenshealth.gov/pregnancy/youre-pregnant-now-what/stages-pregnancy
What Does It Mean to Have a Full-Term Pregnancy? (verywellfamily.com)

Physiologically Based Pharmacokinetic Modelling (PBPK)

- Integrate physiological, biochemical and physical chemical information
- Estimate kinetics in a target tissue or organ (effect compartment)
- Evaluate the effect of various intrinsic (age, race, gender, disease, etc.) and extrinsic (DDI, environment, smoking, etc.) factors on drug exposure and response
- Model variability and uncertainty

User friendly software,
- SimCYP
- PK-Sim
- SimulationPlus



Learn, Confirm, Predict Approach!

Clin Pharmacol Ther. 2011 89:259-67

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PBPK, how often? PubMed

National Library of Medicine
National Center for Biotechnology Information

Log in

PubMed.gov

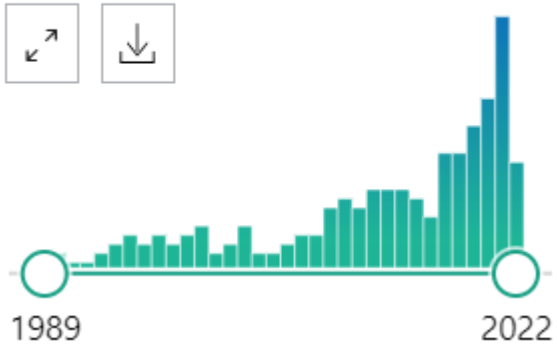
pbpk pregnancy

Search

Advanced Create alert Create RSS User Guide

168 results

RESULTS BY YEAR



Pharmacometrics in **pregnancy**: An unmet need.
Ke AB, Rostami-Hodjegan A, Zhao P, Unadkat JD.
Annu Rev Pharmacol Toxicol. 2014;54:53-69. doi: 10.1146/annurev-pharmtox-011613-140009.
PMID: 24392692 Review.

Model-Informed Dose Optimization in **Pregnancy**.
Chaphekar N, Caritis S, Venkataramanan R.
J Clin Pharmacol. 2020 Oct;60 Suppl 1:S63-S76. doi: 10.1002/jcph.1777.
PMID: 33205432 Review.

Physiologically Based Pharmacokinetics Model in **Pregnancy**: A Regulatory Perspective on Model Evaluation.
Coppola P, Kerwash E, Cole S.

79 results

Filters applied: Associated data. Clear all

ARTICLE TYPE

- [ ] Books and Documents
- [ ] Clinical Trial
- [ ] Meta-Analysis
- [ ] Randomized Controlled Trial
- [ ] Review
- [ ] Systematic Review

Found 1 result for *pbpk pregnancy* Save Em

Filters applied: Clinical Trial. Clear all

Clinical Trial > J Subst Abuse Treat. 2021 Nov;130:108521. doi: 10.1016/j.jsat.2021.108521. Epub 2021 Jun 3.

Precision dosing of methadone during pregnancy: A pharmacokinetics virtual clinical trials study

Raj K S Badhan [1], Rosalind Gittins [2]

Affiliations + expand
PMID: 34118695 DOI: 10.1016/j.jsat.2021.108521

Found 1 result for *pbpk pregnancy* Save Email

Filters applied: Meta-Analysis. Clear all

Meta-Analysis > Environ Health Perspect. 2015 Dec;123(12):1317-24. doi: 10.1289/ehp.1408837. Epub 2015 May 22.

Associations of Perfluoroalkyl Substances (PFAS) with Lower Birth Weight: An Evaluation of Potential Confounding by Glomerular Filtration Rate Using a Physiologically Based Pharmacokinetic Model (PBPK)

Marc-André Verner [1], Anne E Loccisano, Nils-Halvdan Morken, Miyoung Yoon, Huali Wu, Robin McDougall, Mildred Maisonet, Michele Marcus, Reiko Kishi, Chihiro Miyashita, Mei-Huei Chen, Wu-Shiun Hsieh, Melvin E Andersen, Harvey J Clewell 3rd, Matthew P Longnecker

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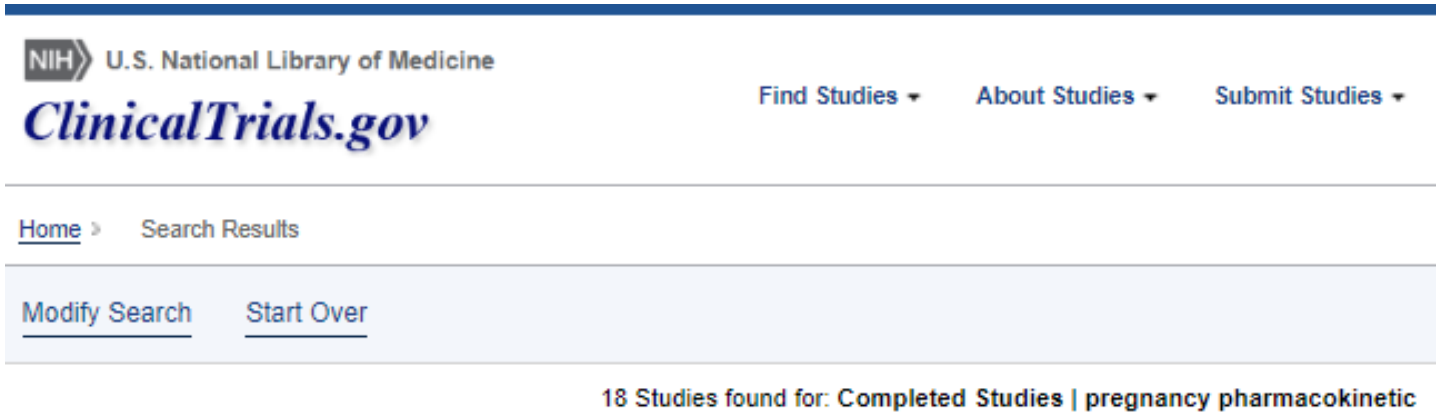
PBPK, how often? Source of PK Clinicaltrial.gov

Infection, pregnancy related etc, n=35 for ongoing, recruiting and completed



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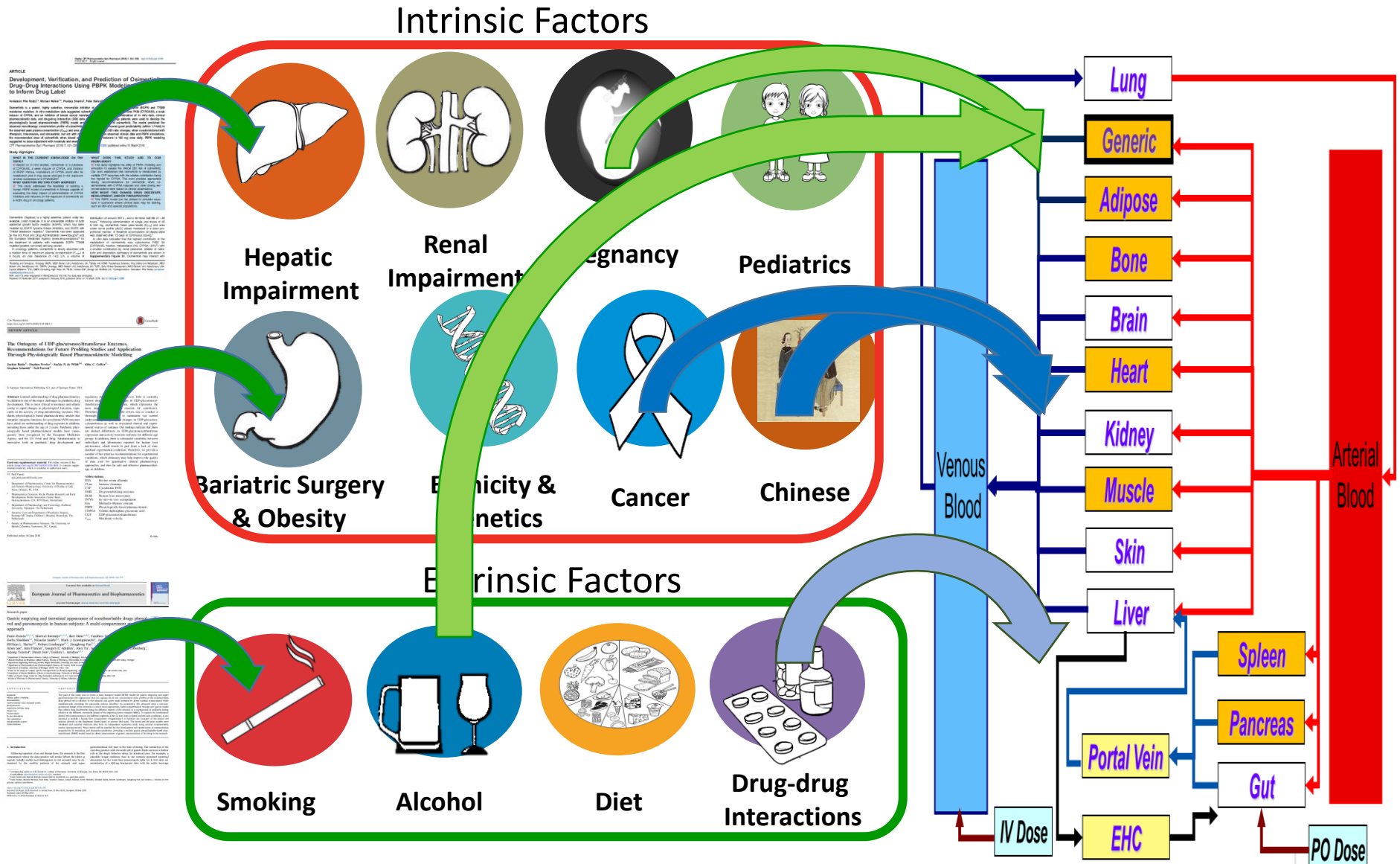
Integrating knowledge in PBPK to EXTRAPOLATE!



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Pharmacotherapy during pregnancy/Lactation - status

- Total avoidance of pharmacological treatments is often not feasible during pregnancy.
  - Pregnancy-related conditions (hypertension, gestational diabetes)
  - breastfeeding-related conditions (mastitis, cracks, lesions)
  - Chronic conditions (e.g., asthma, allergy, epilepsy, depression, HIV/infections)

- Fixed non-pregnant dose does not provide the required efficacy.
- Knowledge of proper dosing is required to prevent poor disease control, fetal /neonatal outcomes and teratogenic effects, …, etc.

- Many drug labels advise not to take many drugs during pregnancy due to the absence of reliable safety data (~ 25% prescribed drugs use during pregnancy are off label and based on safety data from non-pregnant subjects).

- Pregnancy/Lactation studies have been performed in the post-marketing settings

  → delays in drugs availability to pregnant/breastfeeding women

Regulatory considerations

Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

October 2004
Clinical Pharmacology

Postapproval Pregnancy Safety Studies

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

May 2019
Clinical/Medical

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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

April 2018
Clinical/Medical
Revision 1

Clinical Lactation Studies: Considerations for Study Design

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

May 2019
Clinical/Medical

European Medicines Agency

London, 14 November 2005
EMEA/CHMP/313666/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON

THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY:

NEED FOR POST-AUTHORISATION DATA

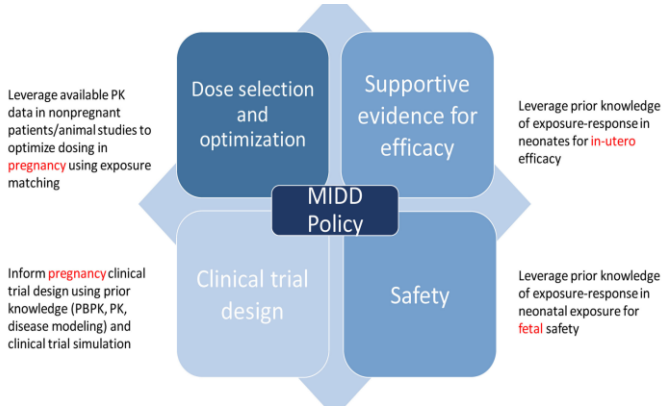
https://www.ema.europa.eu/en/events/workshop-benefit-risk-medicines-used-during-pregnancy-breastfeeding

Regulatory Considerations for the Mother, Fetus and Neonate in Fetal Pharmacology Modeling

frontiers in Pediatrics

*Dionna J. Green[1], Kyunghun Park[2], Varsha Bhatt-Mehta[2], Donna Snyder[1] and Gilbert J. Burckart[2]**

[1] Office of Pediatric Therapeutics, Office of the Commissioner, US Food and Drug Administration, Silver Spring, MD, United States, [2] Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, United States



Physiologically Based Pharmacokinetics Model in Pregnancy: A Regulatory Perspective on Model Evaluation

frontiers in Pediatrics

Paola Coppola, Essam Kerwash and Susan Cole*

Medicines and Healthcare Products Regulatory Agency, London, United Kingdom

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Challenges in Pregnancy PK/PD Clinical Trial Design

Physiological Variability

- Change in enzyme/transporters with gestational age
- Return to baseline
- Growth of the feto-placental unit
- Body size metrics

Enrolment Difficulties

- Usually enrolling ill (target population) pregnancy (HV is unethical unless for vaccine trial)
- Rare disorders: getting enough patients enrolled to satisfy statistical requirements

Choice of Pharmacodynamic Endpoints

- Sensitive, robust, and clinically relevant biomarkers validated in non-pregnant male adult male subjects can be different in women during perinatal period
- Non-invasive biomarkers only

Challenges in Determining Dosing Regimen

- Traditional extrapolation from adult? Use WT, BSA or …?

Sparse Sampling vs. Intensive Sampling

- often sparse sampling in pregnancy clinical studies

Safety monitoring

Only in the duration of the pregnancy

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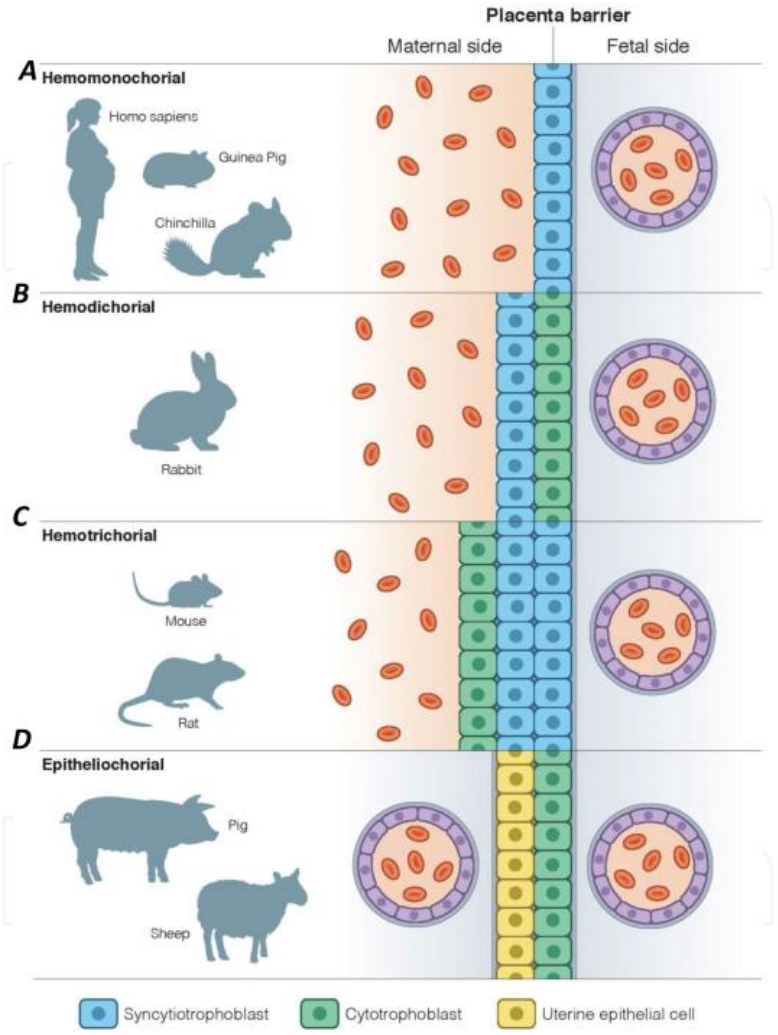
Animal Models of Fetal Medicine and Obstetrics

Table 1 shows the average gestation length, number of fetuses, maternal weight, neonate weight and the placental barrier type in human and relevant species.

Basal gestation parameters of the laboratory animals

Animal species *Latin*	Gestation length (days)	Number of fetuses	Maternal pre-pregnancy weight (g)	Neonate weight (g)	Placenta barrier type
Human *Homo sapiens*	266	1	5900	3183	Hemomonochorial villous
Mouse *Mus musculus*	20	5–6	19	1	Hemotrichorial labyrinth
Rat *Rattus norvegicus*	22	9	283	6	Hemotrichorial labyrinth
Guinea pig *Cavia porcellus*	67	3–4	728	80	Hemomonochorial labyrinth
Chinchilla *Chinchilla lanigera*	113	1–2	480	40	Hemomonochorial labyrinth
Rabbit *Oryctolagus cuniculus*	30	5	1591	39	Hemodichorial labyrinth
Sheep *Ovis aries*	153	1–2	39.100	2376	Epitheliochorial
Pig *Sus scrofa*	115	5–14*	84.000*	400–1900*	Epitheliochorial

Data are acquired from the PanTheria database [82].*
Dependent of the breed of pig (domestic pig or mini-pig) [20].



Andersen MD et al., 2018
http://dx.doi.org/10.5772/intechopen.74038

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The role of physiologically-based pharmacokinetic (PBPK) models

- PBPK models combined drug-related data with pregnancy-related physiological changes.
- Impact of inter-individual variability (genotypes, demographics, enzyme activity) of subjects can be addressed.
- PBPK model have been applied recently to*
  - predict maternal and umbilical drug levels
  - evaluate the requirement of dose adjustment or proposing new dosing regimen during pregnancy

Drugs	Pregnancy PBPK application	Ref
Chloroquine	proposing a dosing regimens for prevention of Zika Virus disease	Olafuyi & Badhan 2019
Darunavir (+ ritonavir)	Dosing optimisation strategy based on predicted umbilical vein concentration	Schalkwijk et al., 2018
Paroxetine	CYP2D6 Genotype-based dose optimization	Almurjan et al., 2020
Piperaquine	Assess the impact of efavirenz or ritonavir on piperaquine in distinct customised HIV infected population (Thailand, Sudan & Papua New Guinea)	Olafuyi et al., 2017
Quetiapine	Dosing optimisation strategy	Badhan & Macfarlane 2020
Efavirenz	CYP2B6 Genotype-based dose optimization	Chetty et al., 2020

*Abduljalil & Badhan J Pharmacokinet Pharmacodyn 2020 Aug;47(4):319-340.

Pregnancy PBPK model- verifications (CYPs)

Journal of Pharmacokinetics and Pharmacodynamics
https://doi.org/10.1007/s10928-020-09711-2

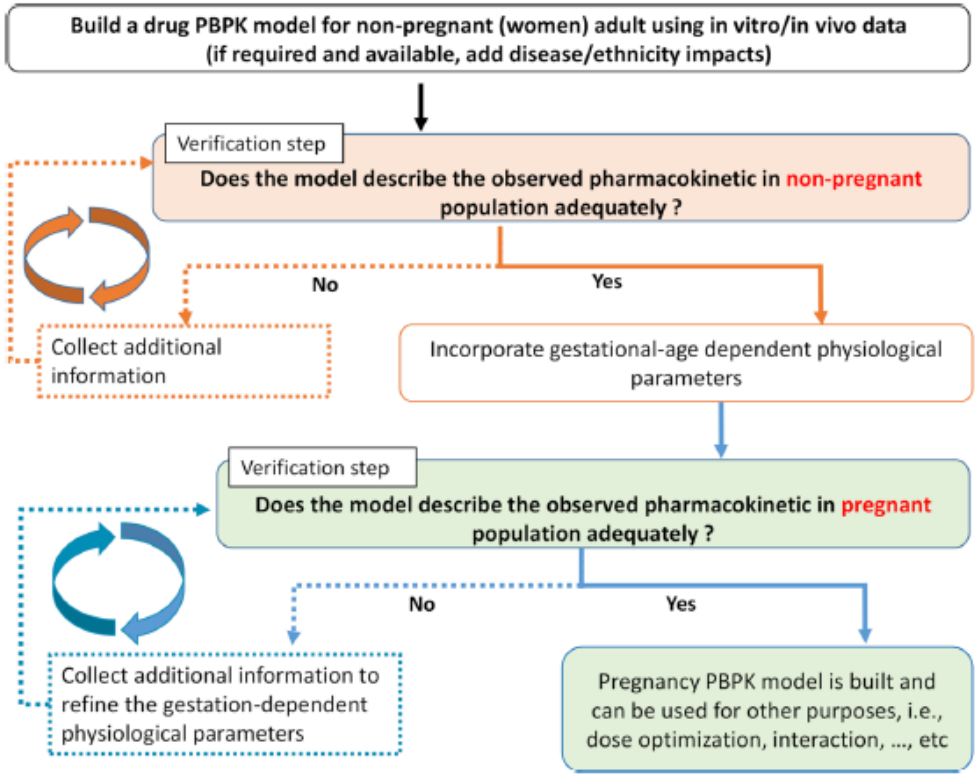
ORIGINAL PAPER

Prediction of maternal pharmacokinetics using physiologically based pharmacokinetic models: assessing the impact of the longitudinal changes in the activity of CYP1A2, CYP2D6 and CYP3A4 enzymes during pregnancy

Khaled Abduljalil[1] · Amita Pansari[1] · Masoud Jamei[1]

Received: 28 July 2020 / Accepted: 11 August 2020

- ✓ Caffeine
- ✓ Theophylline
- ✓ Metoprolol,
- ✓ Propranolol
- ✓ Paroxetine
- ✓ Midazolam
- ✓ Nifedipine
- ✓ Rilpivirine



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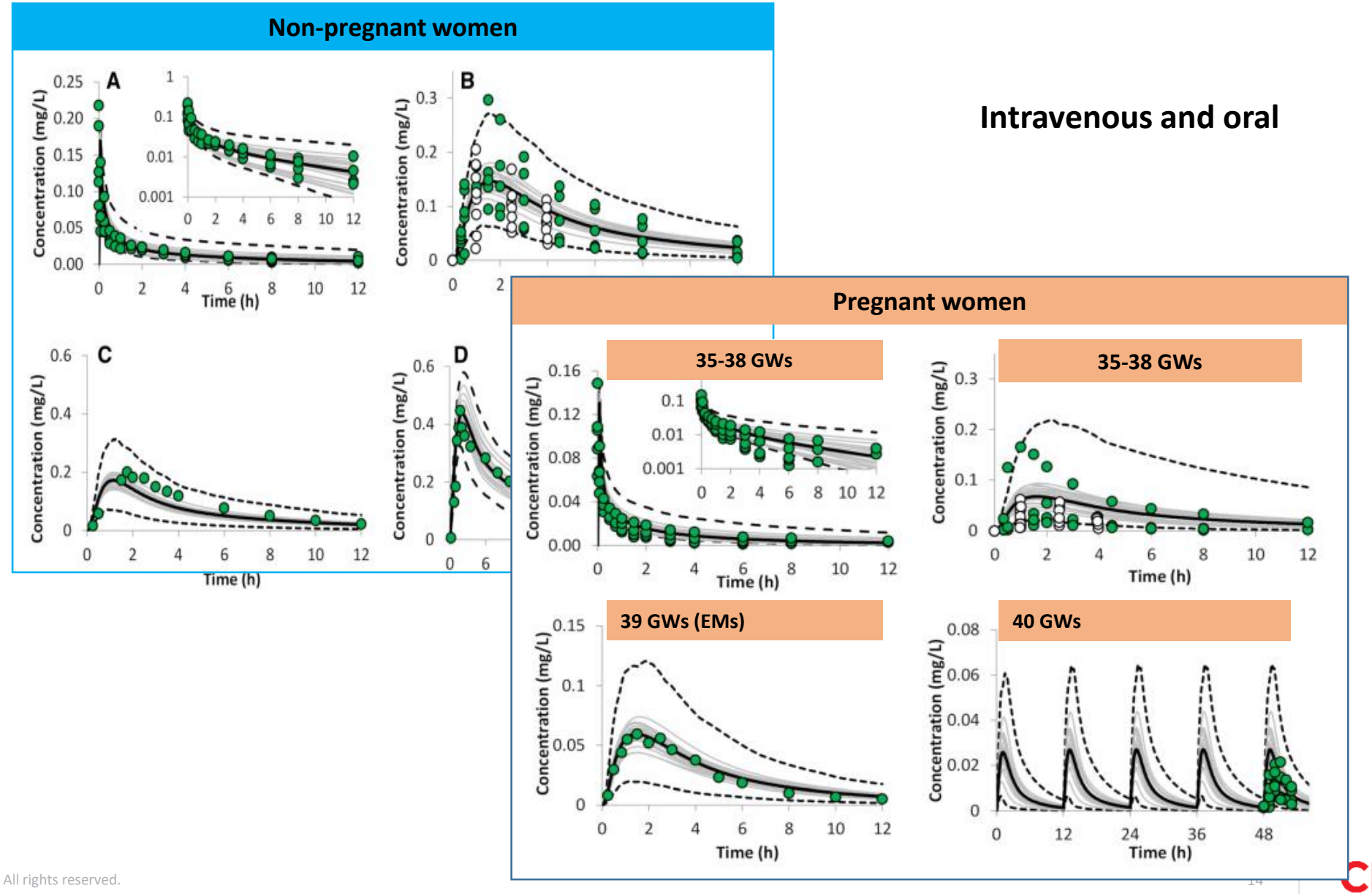
Metoprolol PK during Pregnancy (CYP2D6)



Intravenous and oral

Transporter example: Metformin PK during Pregnancy

Application of physiologically based pharmacokinetic modeling to predict drug disposition in pregnant populations

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[1] Samuel J. and Joan B. Williamson Institute for Pharmacometrics, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, New York, USA

[2] KinderPharm LLC, Exton, Pennsylvania, USA

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David R. Taft, Professor of Pharmaceutics, Division of Pharmaceutical Sciences, Long Island University, 75 DeKalb Avenue, Brooklyn, NY 11201, USA.
Email: dtaft@liu.edu

Abstract

Pregnancy is
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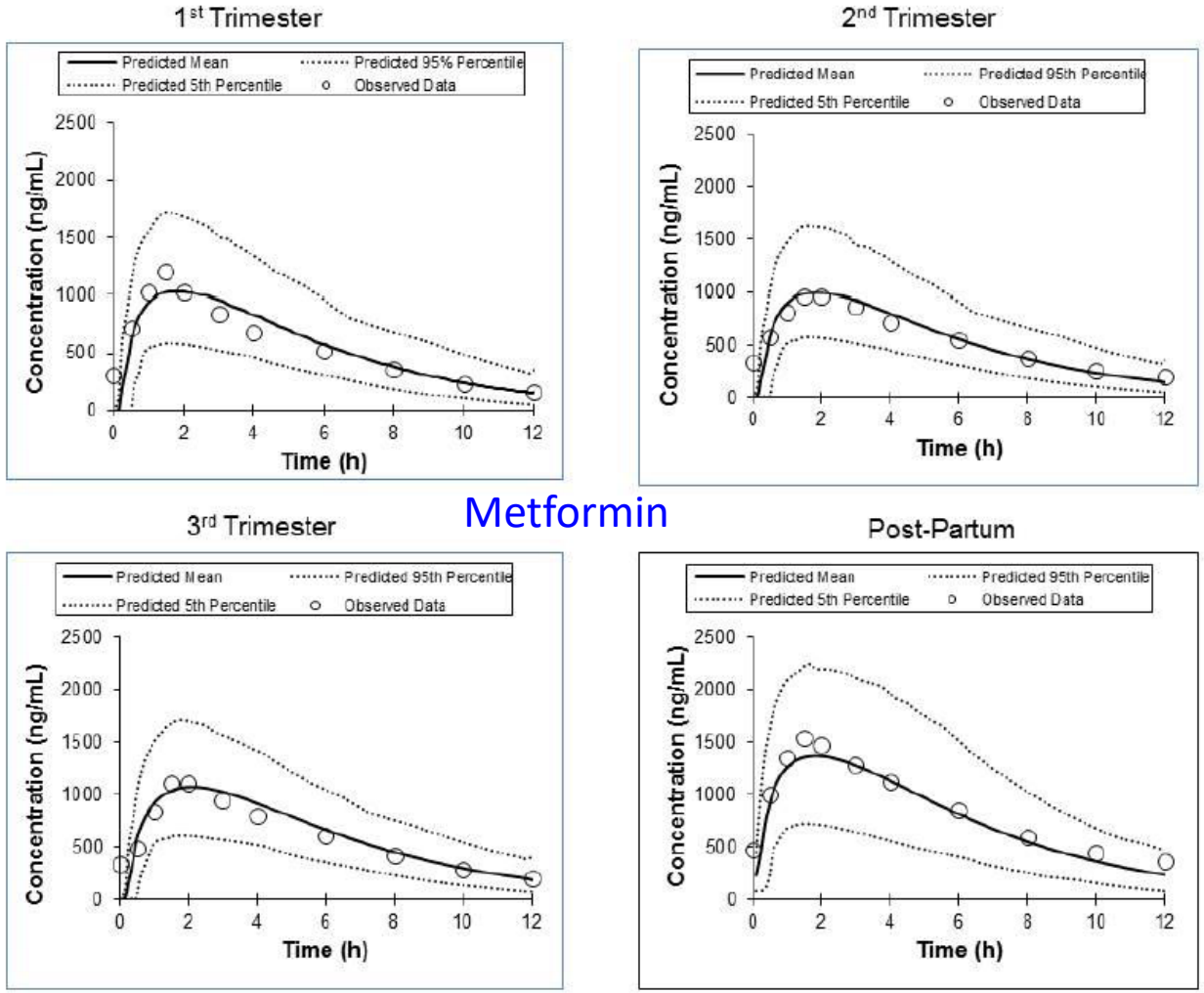
Metformin is a substrate for several transporters – OCT1, OCT2, MATEs.

Pregnancy ontogeny for OCT2 considered in model



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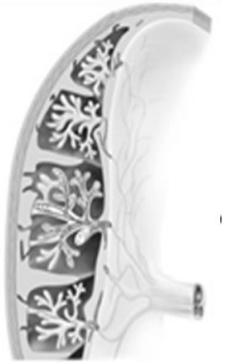
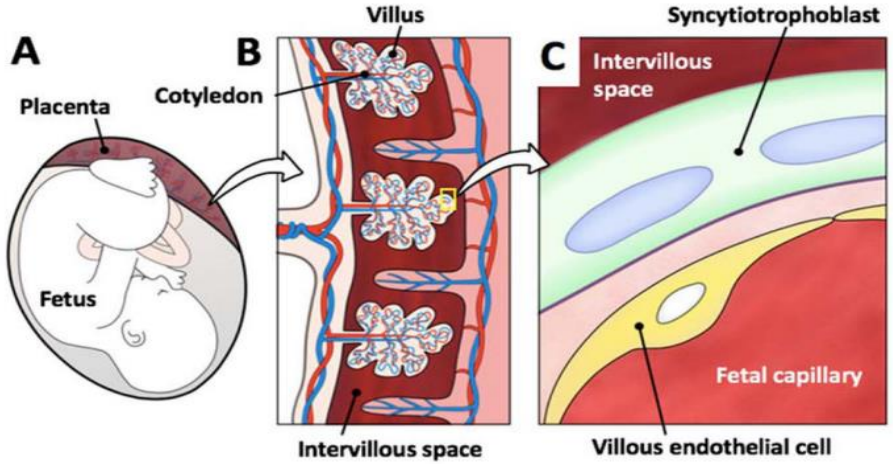
Maternal-Placental-Fetal drug transfer



- Maternal circulation
- Maternal drug metabolism
- Placental transport
- Placental metabolism
- Umbilical cord/Fetal circulation
- Fetal metabolism, renal excretion
- Amniotic fluid



Blundell et al. Lab Chip. 2016 August 2; 16(16): 3065–3073.

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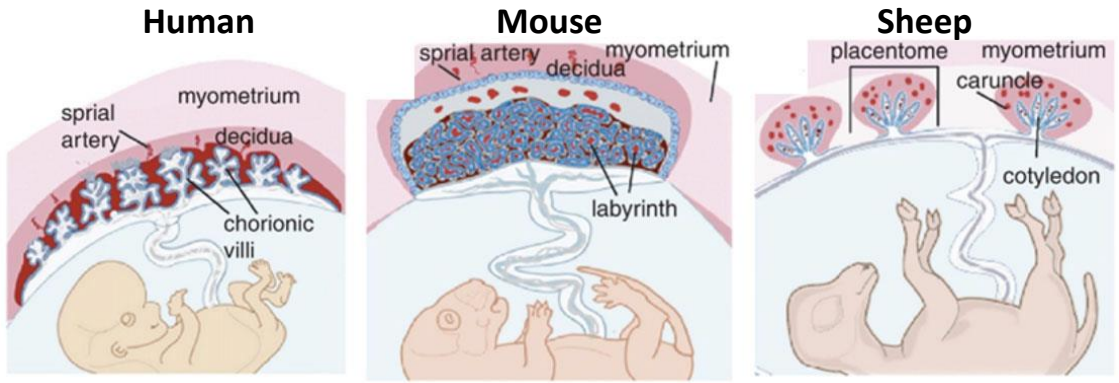
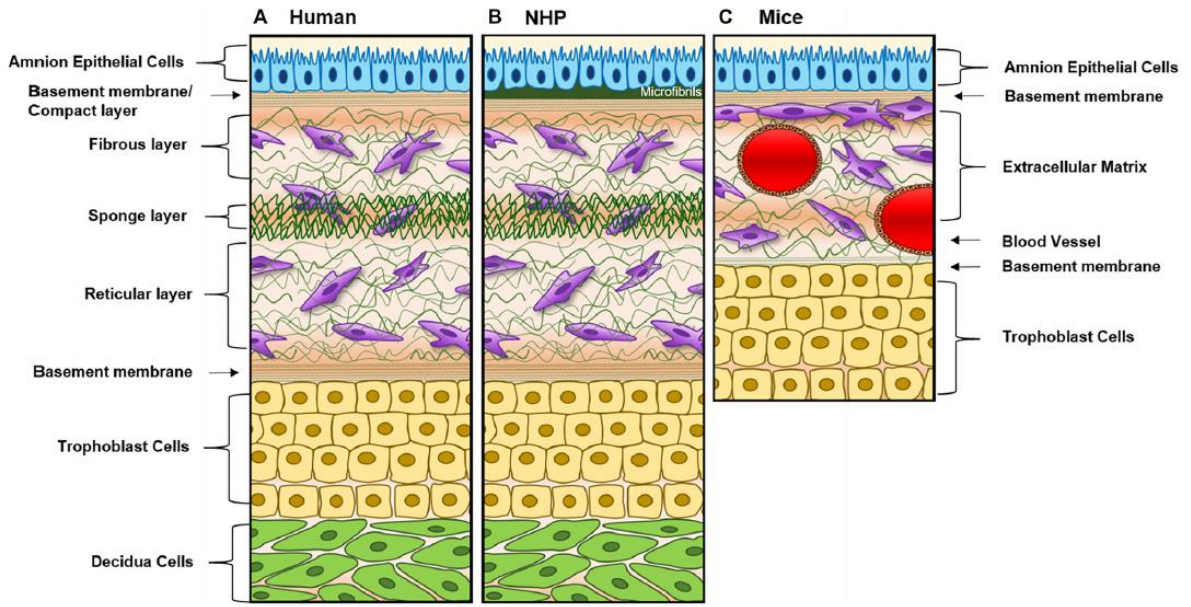
Animal vs Human: Placenta & Fetus

Placenta



Pemathilaka et al. 2019. Interface Focus 9: 20190031.

Fetal membrane



Richardson et al. (2020) Front. Physiol. 11:715.

Metabolic differences??: For example, thalidomide is a severe teratogen in humans causing phocomelia, but not in rats.

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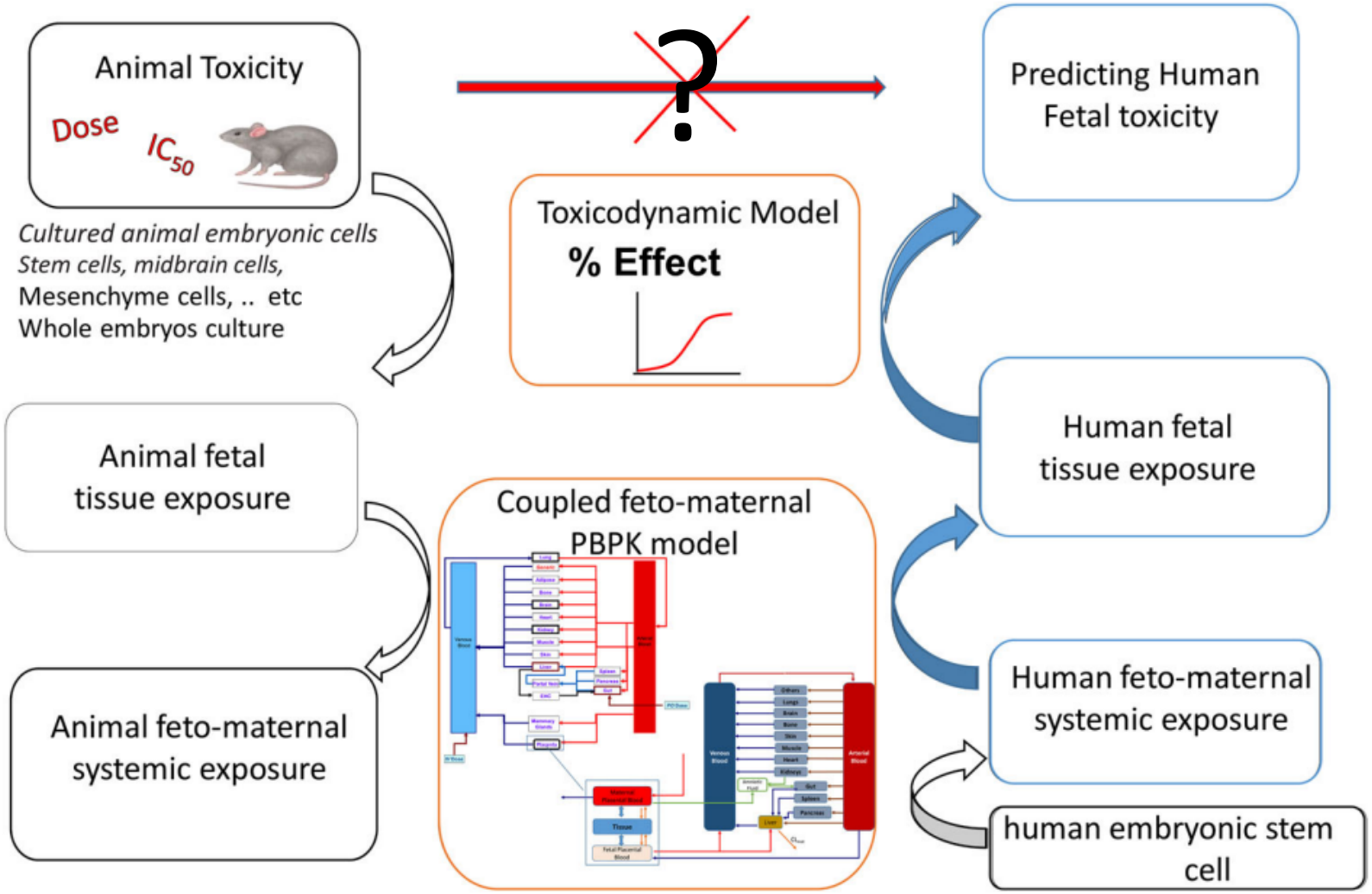
PBPK model framework



Abduljalil et al. Clin Pharmacokinet (2018) 57:1149–1171

Model application to assess fetal exposure: vital for safety assessment

Application of a Physiologically Based Pharmacokinetic Approach to Predict Theophylline Pharmacokinetics Using Virtual Non-Pregnant, Pregnant, Fetal, Breast-Feeding, and Neonatal Populations

Khaled Abduljalil, Iain Gardner and Masoud Jamei*

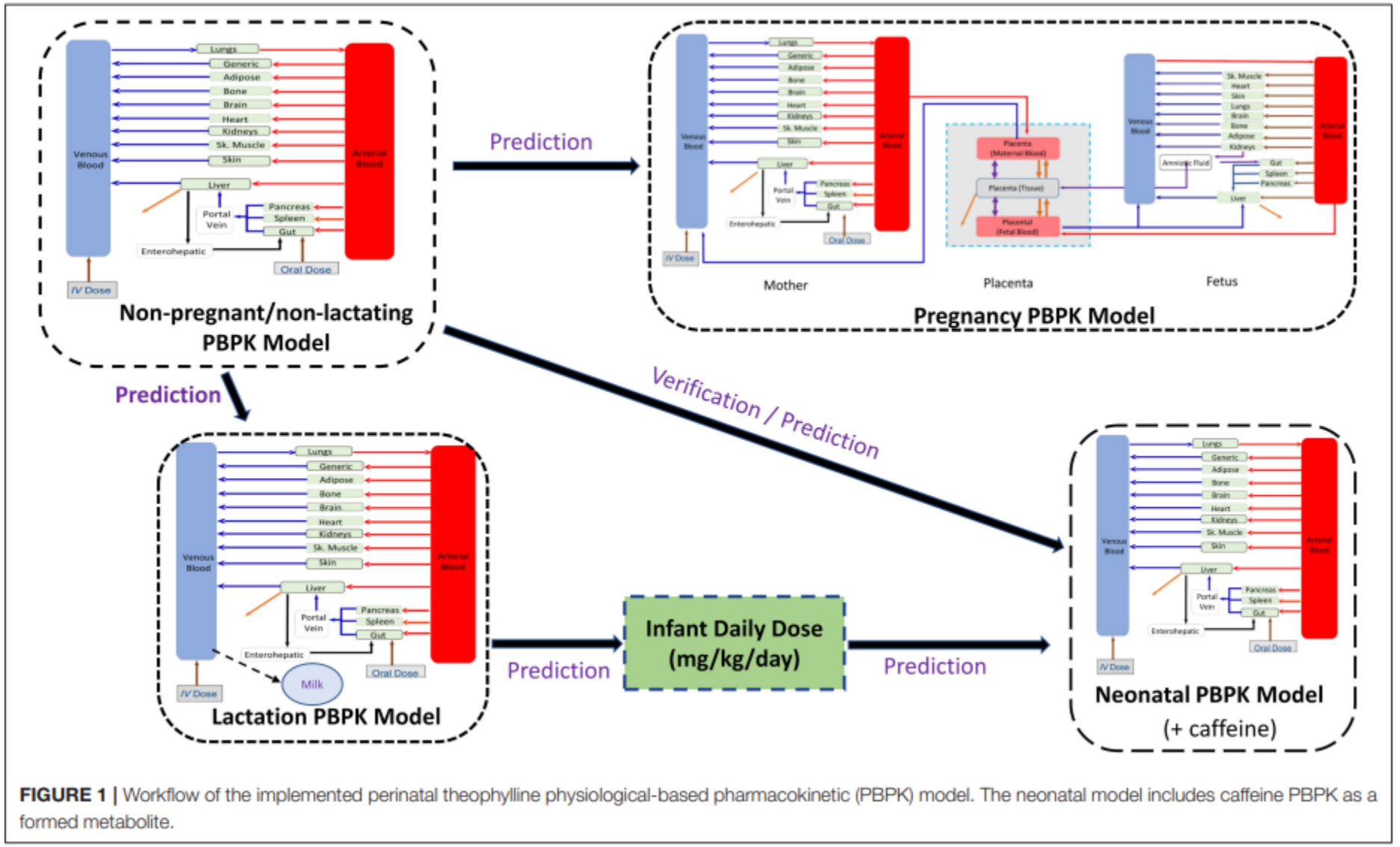


FIGURE 1 | Workflow of the implemented perinatal theophylline physiological-based pharmacokinetic (PBPK) model. The neonatal model includes caffeine PBPK as a formed metabolite.

https://www.frontiersin.org/articles/10.3389/fped.2022.840710/full?&utm_source=Email_to_authors_&utm_medium=Email&utm_content=T1_11.5e1_author&utm_campaign=Email_publication&field=&journalName=Frontiers_in_Pediatrics&id=840710

Non-pregnancy calibration

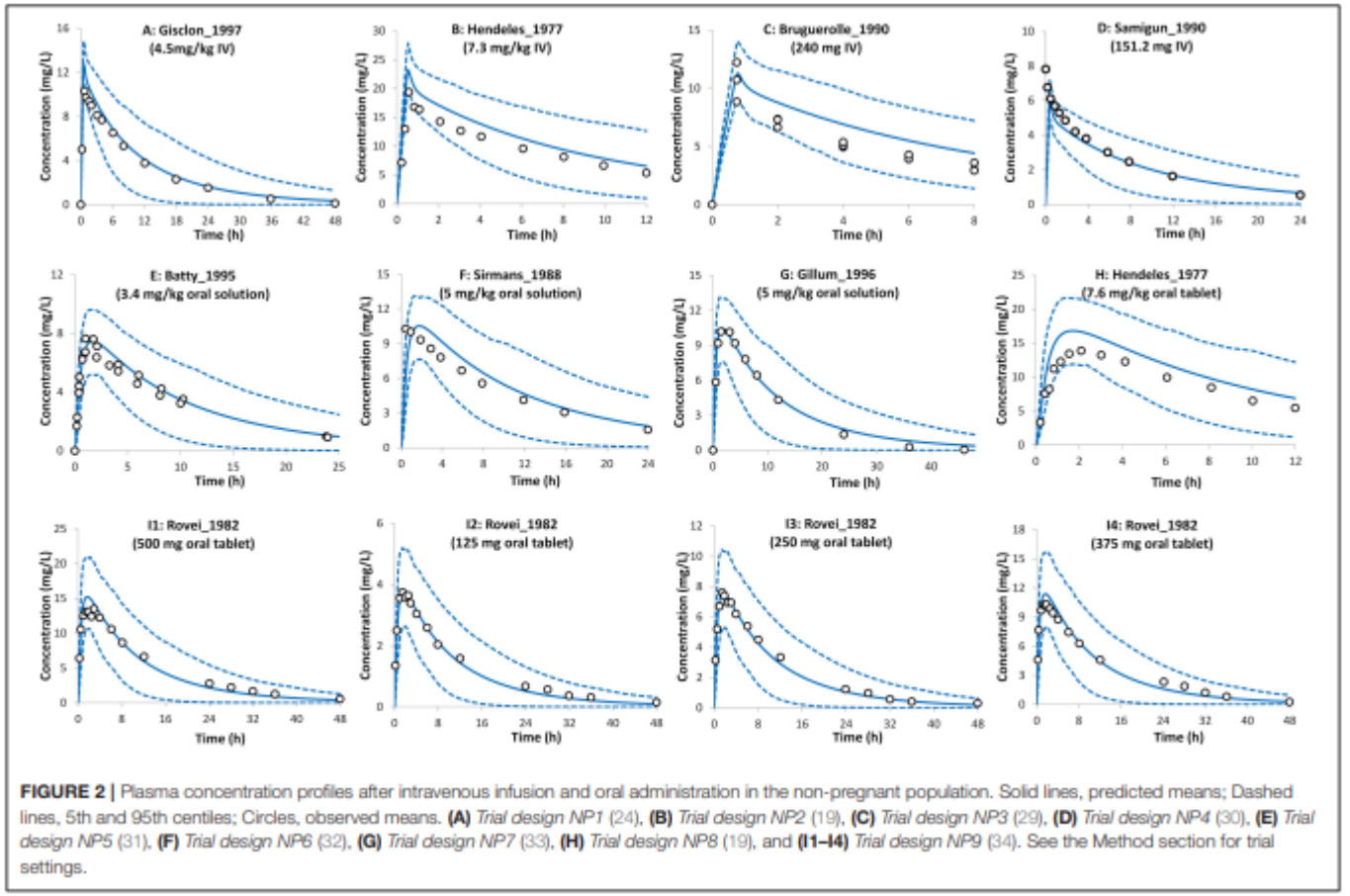


FIGURE 2 | Plasma concentration profiles after intravenous infusion and oral administration in the non-pregnant population. Solid lines, predicted means; Dashed lines, 5th and 95th centiles; Circles, observed means. **(A)** *Trial design NP1* (24), **(B)** *Trial design NP2* (19), **(C)** *Trial design NP3* (29), **(D)** *Trial design NP4* (30), **(E)** *Trial design NP5* (31), **(F)** *Trial design NP6* (32), **(G)** *Trial design NP7* (33), **(H)** *Trial design NP8* (19), and **(I1–I4)** *Trial design NP9* (34). See the Method section for trial settings.

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Simulation

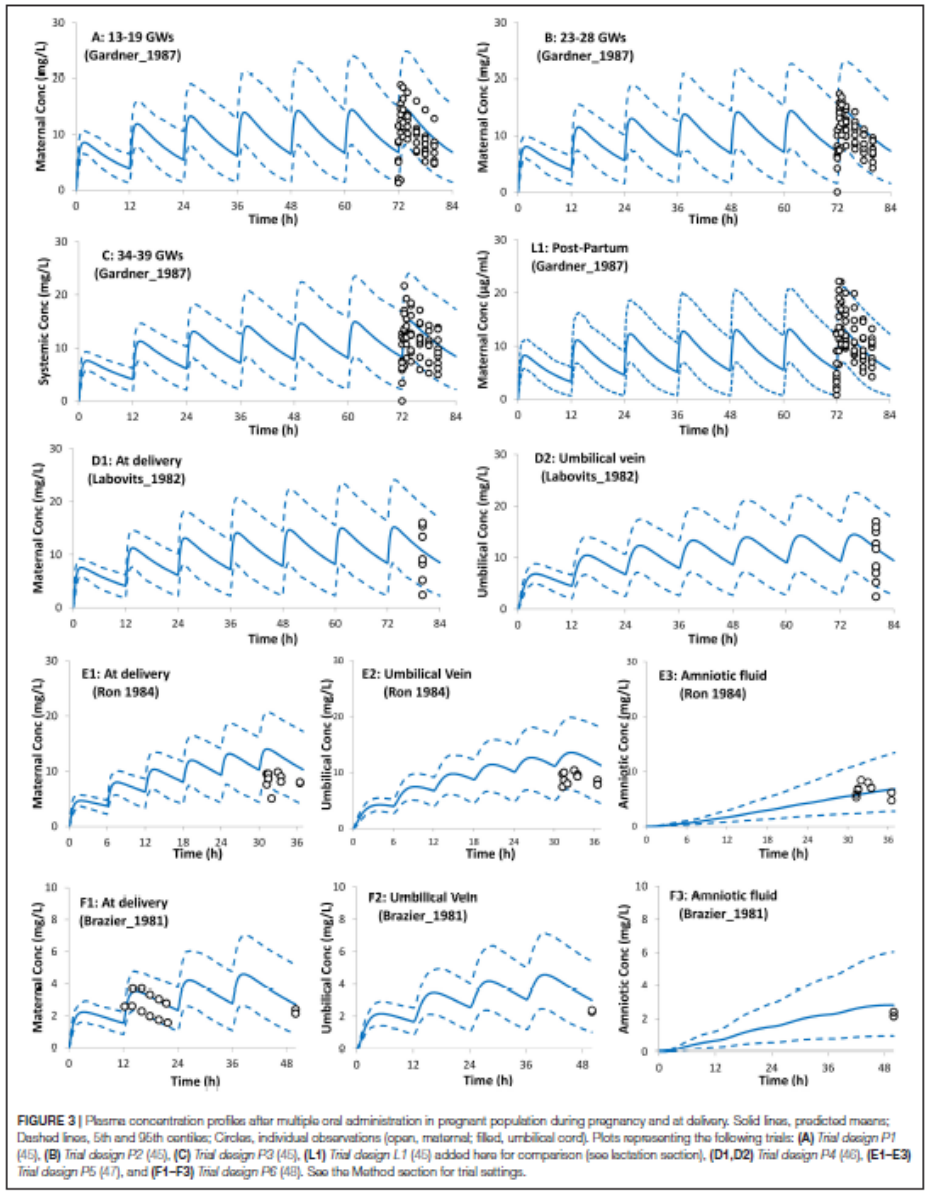

FIGURE 3 | Plasma concentration profiles after multiple oral administration in pregnant population during pregnancy and at delivery. Solid lines, predicted means; Dashed lines, 5th and 95th centiles; Circles, individual observations (open, maternal; filled, umbilical cord). Plots representing the following trials: **(A)** *Trial design P1* (45), **(B)** *Trial design P2* (46), **(C)** *Trial design P3* (45), **(L1)** *Trial design L1* (45) added here for comparison (see lactation section), **(D1,D2)** *Trial design P4* (46), **(E1–E3)** *Trial design P5* (47), and **(F1–F3)** *Trial design P6* (48). See the Method section for trial settings.

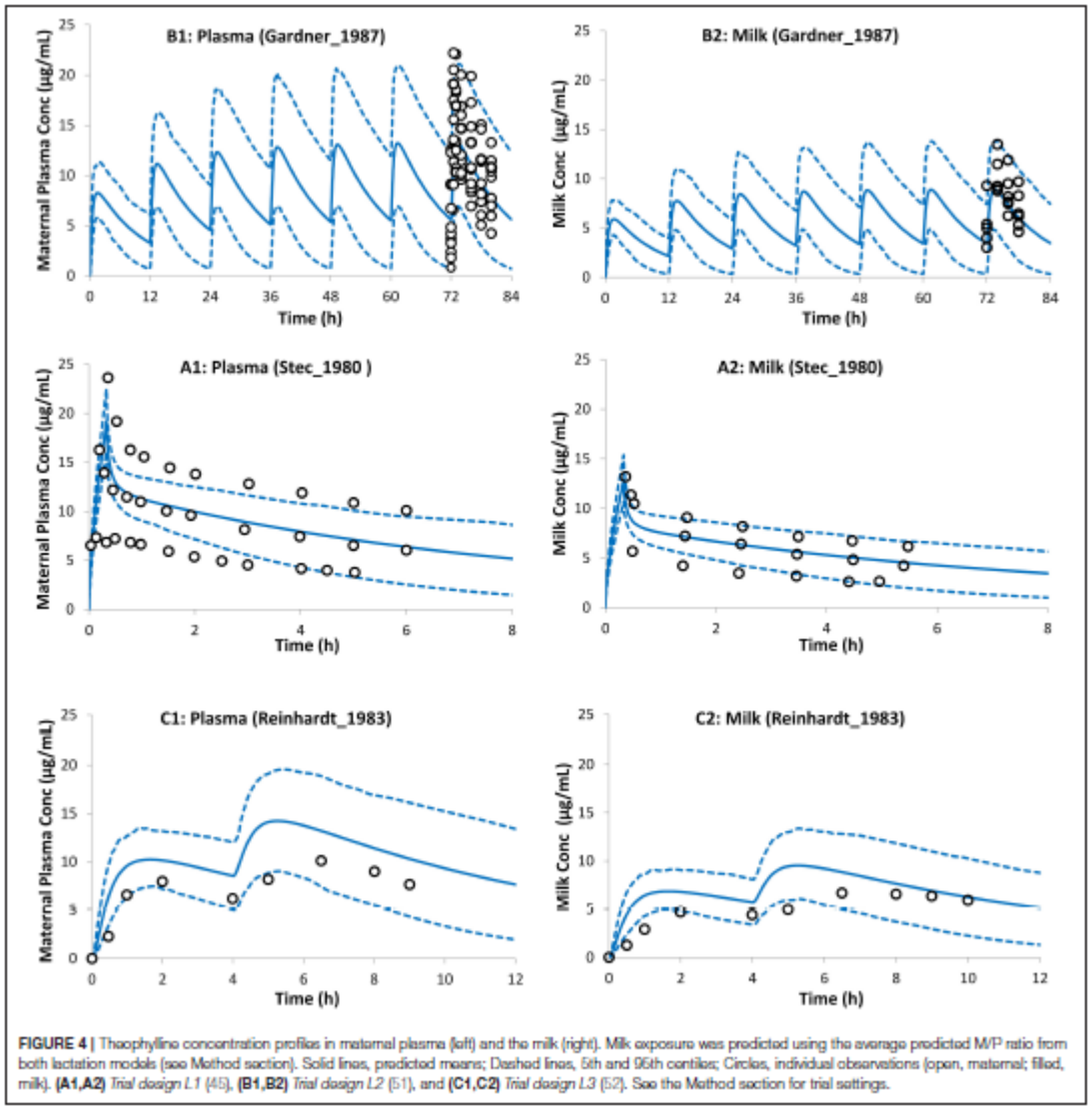

FIGURE 4 | Theophylline concentration profiles in maternal plasma (left) and the milk (right). Milk exposure was predicted using the average predicted M/P ratio from both lactation models (see Method section). Solid lines, predicted means; Dashed lines, 5th and 95th centiles; Circles, individual observations (open, maternal; filled, milk). **(A1,A2)** *Trial design L1* (45), **(B1,B2)** *Trial design L2* (51), and **(C1,C2)** *Trial design L3* (52). See the Method section for trial settings.

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Design evaluations

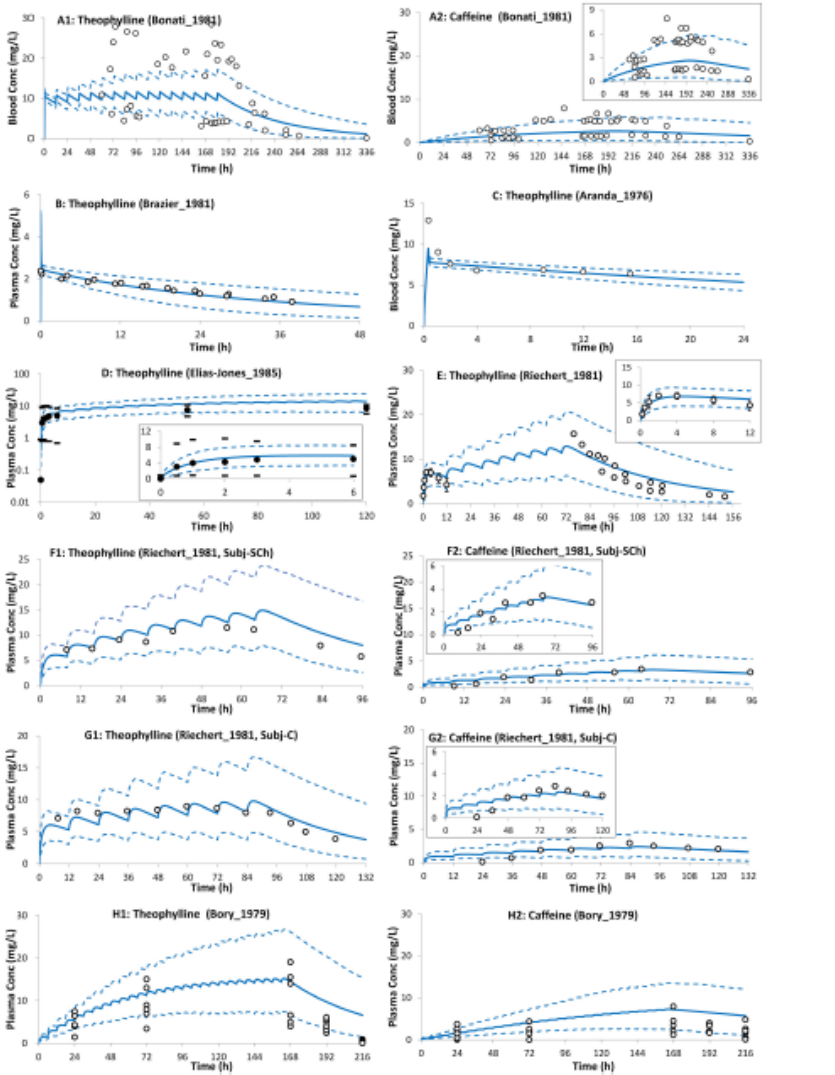

FIGURE 5 | Theophylline (and formed caffeine) concentration profiles in neonates after intravenous **(A–C)** and oral **(D–H)** administration of theophylline. Solid lines, predicted means; Dashed lines, 5th and 95th centiles; closed circles, individual observations; closed circles **(D,E)**, mean; dashes associated with observations in **(D)** represent reported ranges, and bars **(E)**; till 12 h) represent SD. **(A1,A2)** *Trial design N1* (28), **(B)** *Trial design N2* (48), **(C)** *Trial design N3* (57), **(D)** *Trial design N4* (55), **(E)** *Trial design N5* (58), **(F1,F2)** *Trial design N6* (58) subject-Sch, **(G1,G2)** *Trial design N6* (58) subject-C, and **(H1,H2)** *Trial design N7* (27). See the Method section for trial settings.

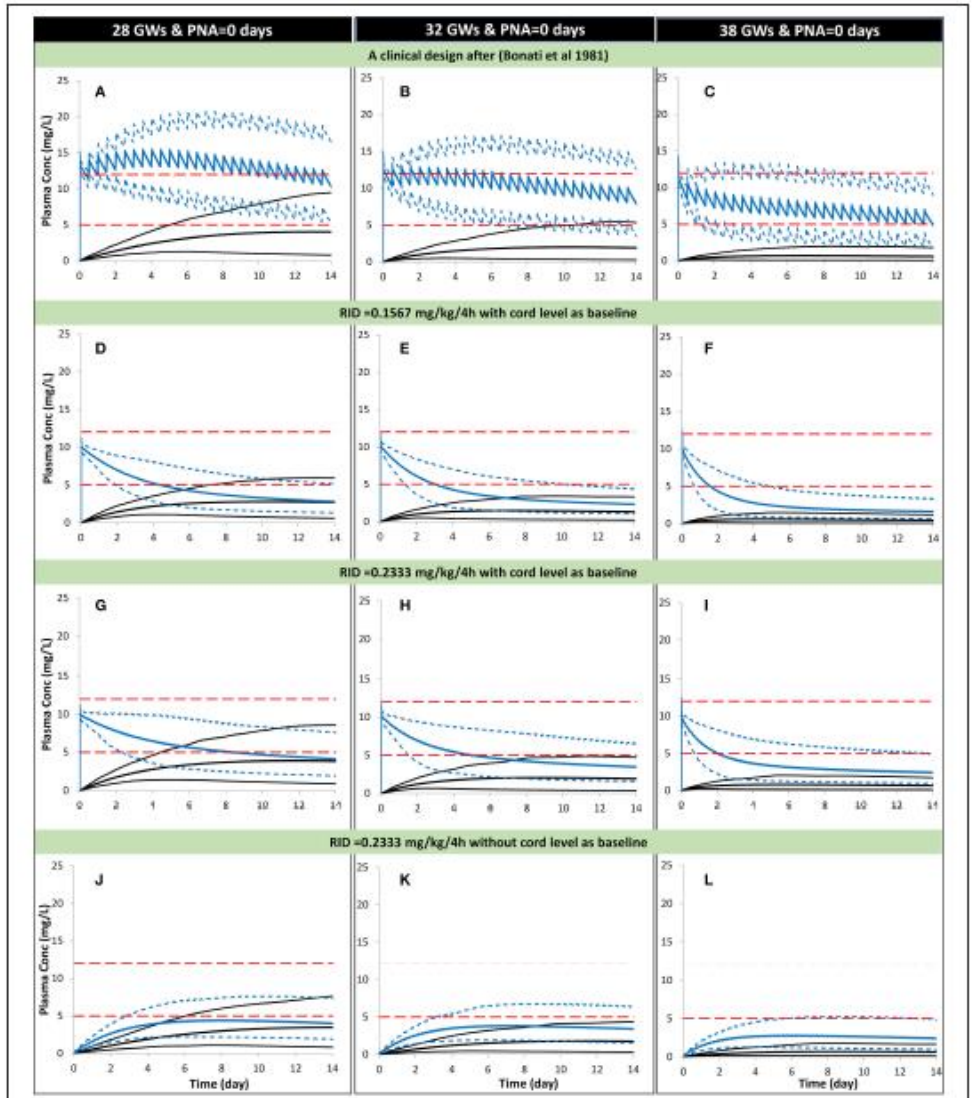

FIGURE 6 | Predicted mean (5th–95th percentiles) neonatal theophylline (and formed caffeine) concentration during the first 2 weeks of life with different gestational weeks. Predicted scenarios: The first three plots show, respectively, theophylline exposure in neonates at birth using a dosage of 30-min infusion of 5 mg/kg as a loading dose followed by 1 h-infusion of 1.1 mg/kg/12 h in 28 **(A)**, 32 **(B)**, and 38 **(C)** GWs according to a clinical study (28). Exposure after oral administration of the calculated theophylline infant dose using milk $C_{avg,ss}$ are shown for 28 **(D)**, 32 **(E)**, and 38 **(F)** GW considering the cord level at birth as a baseline. Exposure after oral administration of the calculated theophylline infant dose using milk $C_{max,ss}$ are shown for 28 **(G)**, 32 **(H)**, and 38 **(I)** GW considering the cord level at birth as a baseline. *(Continued)*

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