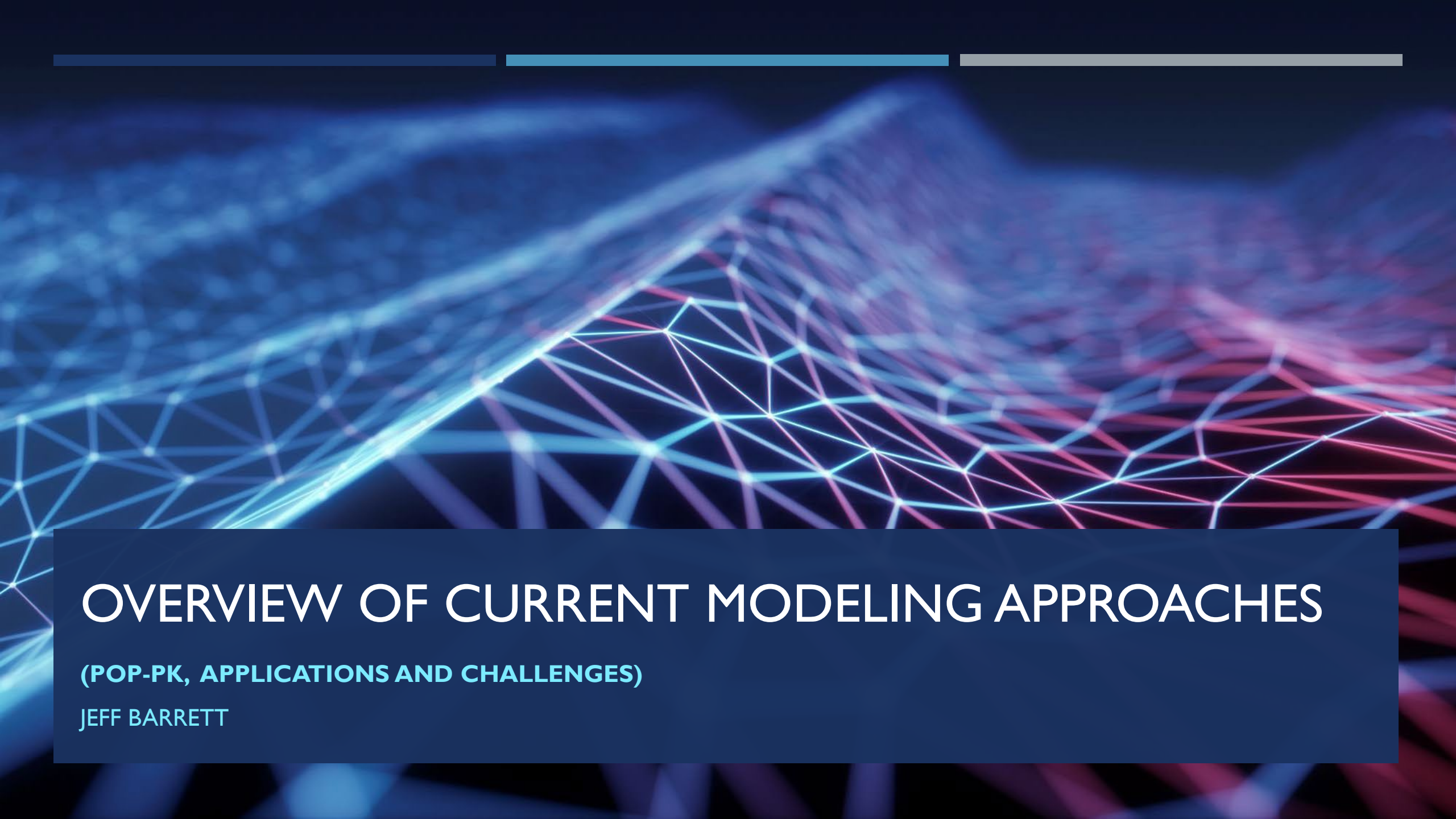

OVERVIEW OF CURRENT MODELING APPROACHES

(POP-PK, APPLICATIONS AND CHALLENGES)

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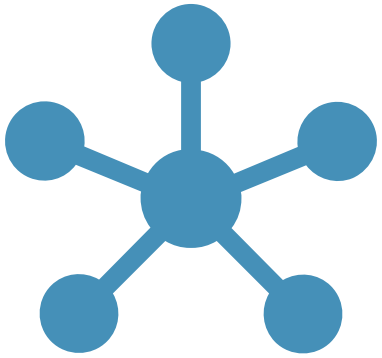
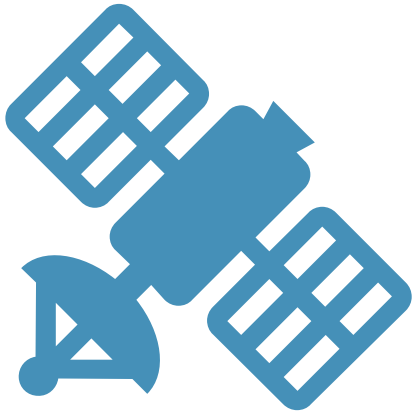
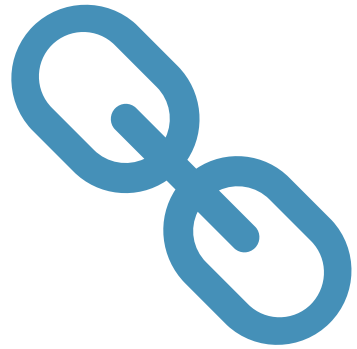


Historical Efforts



What work best and not so much



Tools and approaches for now and the future

MODELING & SIMULATION SUPPORT FOR PREGNANCY TRIALS

HISTORICAL EFFORTS TO SUPPORT PREGNANCY TRIALS

- Design
- Sampling
- Interpretation

- Pregnant women are often excluded from routine clinical trials.
- Consequently, appropriate dosing regimens for majority of drugs are unknown in this population, which may lead to unexpected safety issue or insufficient efficacy in this un-studied population.
- Establishing evidence through the conduct of clinical studies in pregnancy is still a challenge.

THE PROBLEM LANDSCAPE

Scope of the problem	Contributors to the problem
• Inadequate pharmacological studies performed during pregnancy, lactation and postpartum • Limited data on pregnancy mediated changes in drug exposure and response • Optimal dosing for pregnant, lactating, postpartum women unclear for most medications • Impact of drug exposure on fetal growth and development is unclear for almost all medications used during pregnancy • Limited data on drug transfer through breast feeding • Limited incentive for industries (safety—liability issues)	• Pregnancy is an exclusion in most clinical trials • Inadequate funding for clinical pharmacology research in pregnant, lactating and postpartum women • Inadequate number of investigators qualified to perform or engaged in such studies • Inconvenient study designs for participants • Need for innovative sampling techniques and modeling approaches

Chaphekar N, Dodeja P, Shaik IH, Caritis S, Venkataramanan R. Maternal-Fetal Pharmacology of Drugs: A Review of Current Status of the Application of Physiologically Based Pharmacokinetic Models. Front Pediatr. 2021 Nov 3;9:733823. doi: 10.3389/fped.2021.733823. PMID: 34805038; PMCID: PMC8596611.

THE "PROPOSED SOLUTION" LANDSCAPE

Ideal studies	Next best alternatives	Alternate approaches
• Drug exposure studies (Pharmacokinetics over a dosing interval) in first, second, third trimester and post-partum • Drug response studies over a dosing interval (first, second, third trimester and post-partum) • Maternal drug safety assessments (first, second, third trimester and post-partum) • Fetal / Neonatal drug safety assessments (monitoring of neonates and newborn) • Drug excretion in breast milk (total amount excreted in breast milk over a dosing interval)	• Surrogate drug exposure studies (limited sampling strategy or trough level) in first, second, third trimesters and post-partum • Limited drug response studies (first, second, third trimester and post-partum) • Placental (*in vitro*) perfusion studies • Cord blood sampling for fetal exposure assessments • Milk to plasma ratio for drugs in lactating women • Placental perfusion studies • Placenta on a chip study	• Predictions based on probe drug studies for DME and transporters • Population PK modeling • PBPK modeling and simulations

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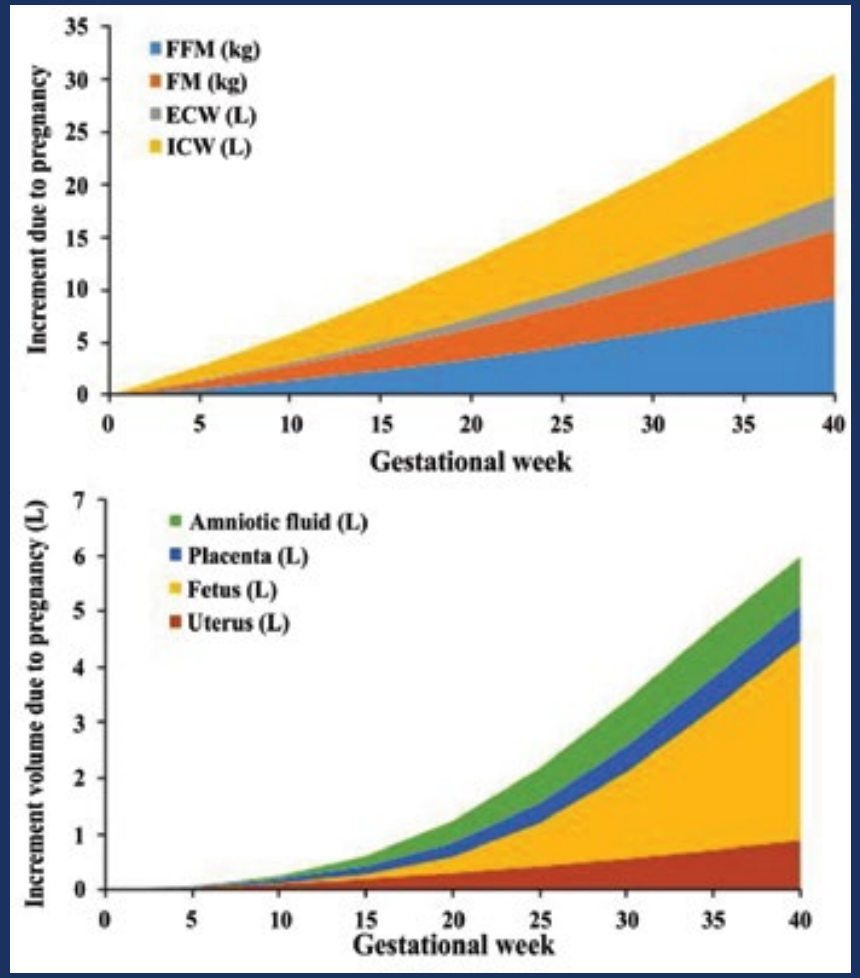
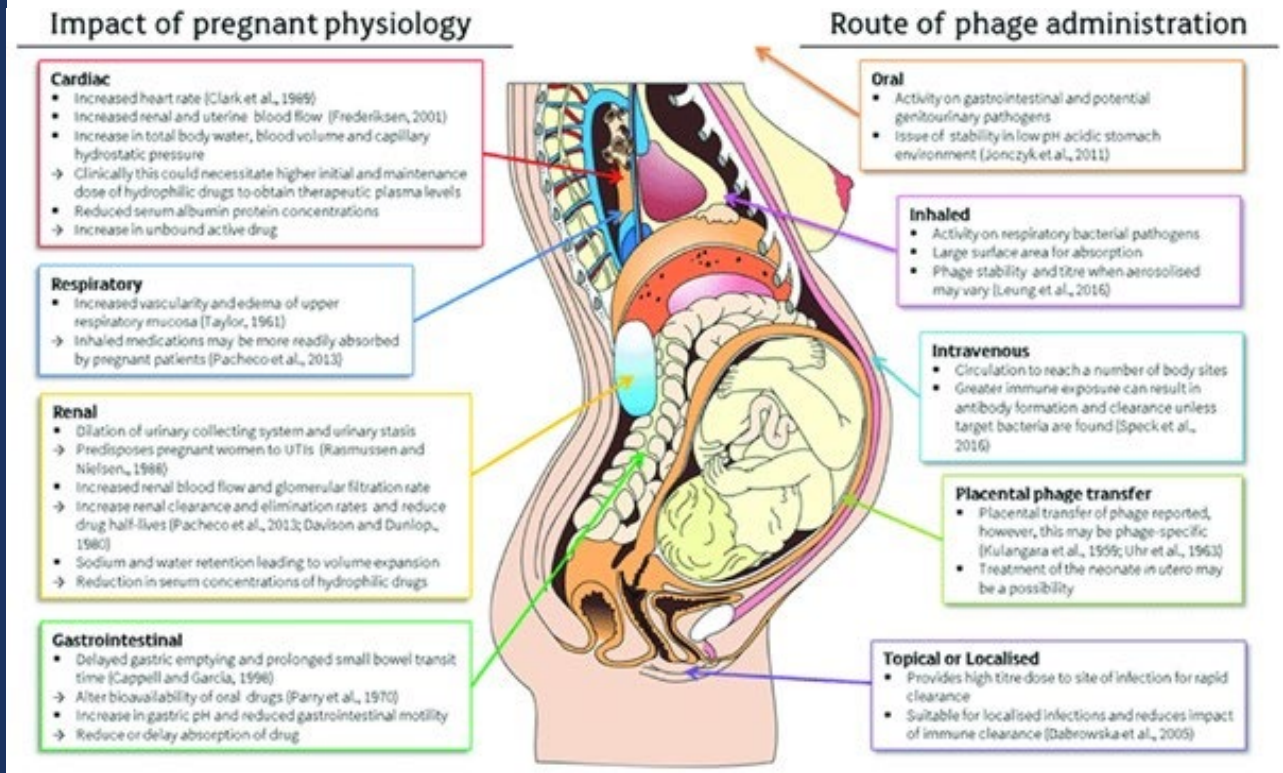
DESIGN CONSIDERATIONS

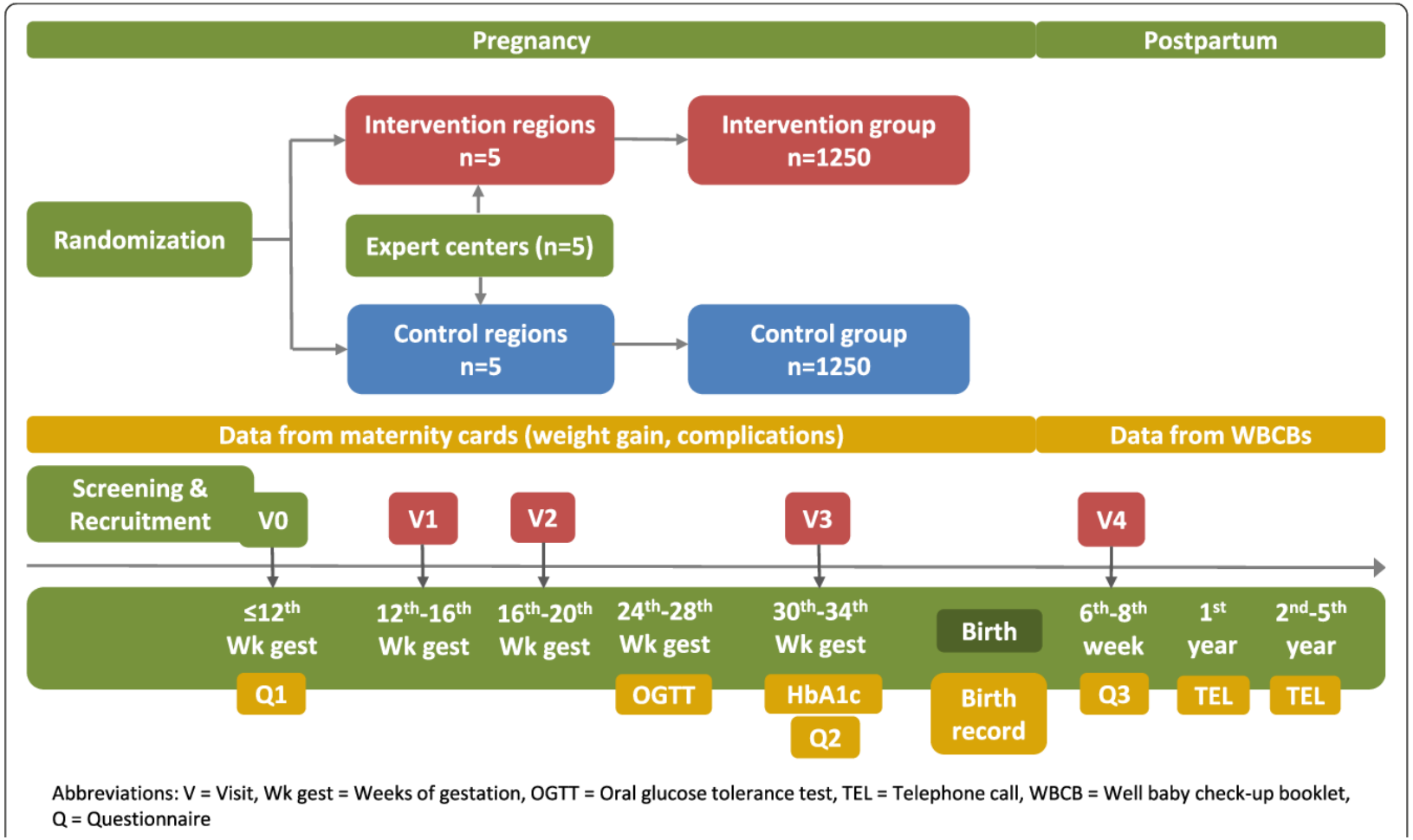


- Who to study?
- When to study?
- How to study?



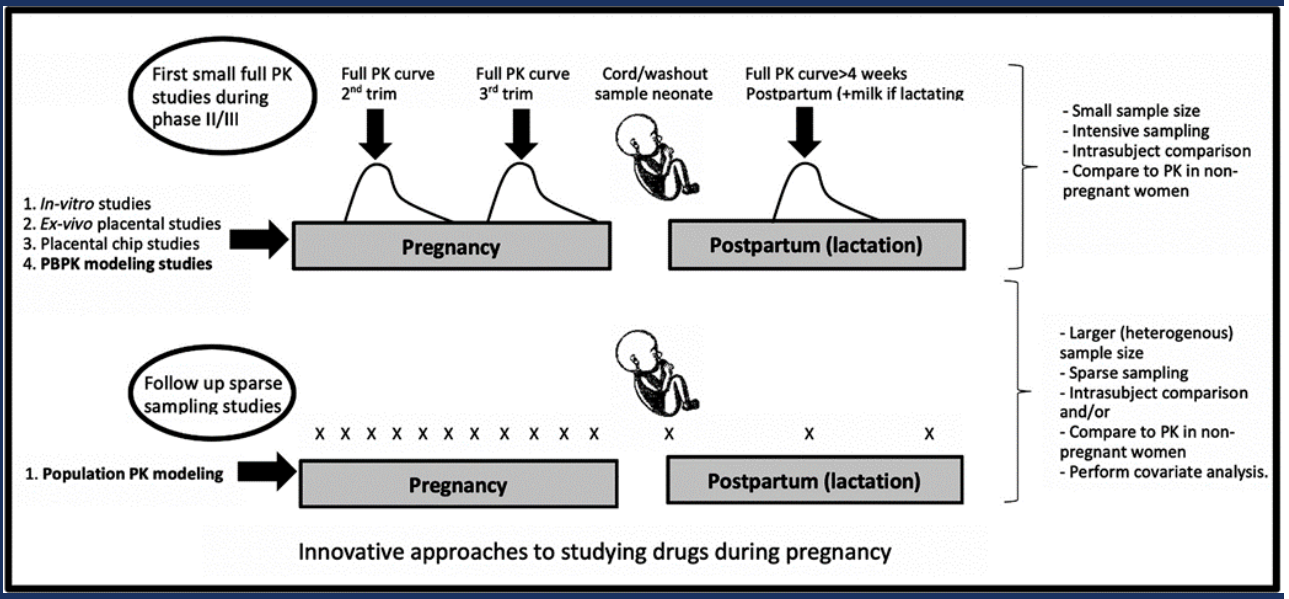
DESIGN CONSIDERATIONS

- Design Flexibility
- Focus on information gaps



Abbreviations: V = Visit, Wk gest = Weeks of gestation, OGTT = Oral glucose tolerance test, TEL = Telephone call, WBCB = Well baby check-up booklet, Q = Questionnaire

SAMPLING



Clin Pharma and Therapeutics, Volume: 110, Issue: 1, Pages: 36-48, First published: 15 September 2020, DOI: (10.1002/cpt.2048)

General Considerations:

- Samples should include plasma or whole blood and urine for assessing the concentration of the parent drug and active metabolites.
- Since plasma protein binding is often reduced during pregnancy, consider calculating unbound drug and metabolites, especially if the extent of plasma protein binding of the drug is high (>80%).
- PD endpoints, including relevant biomarkers and potentially even fetal PD endpoints, can be important.
- Informative study design considerations should be discussed with the FDA prior to study initiation
- Simulations, regardless of model-type, can help.

SAMPLING

General Considerations:

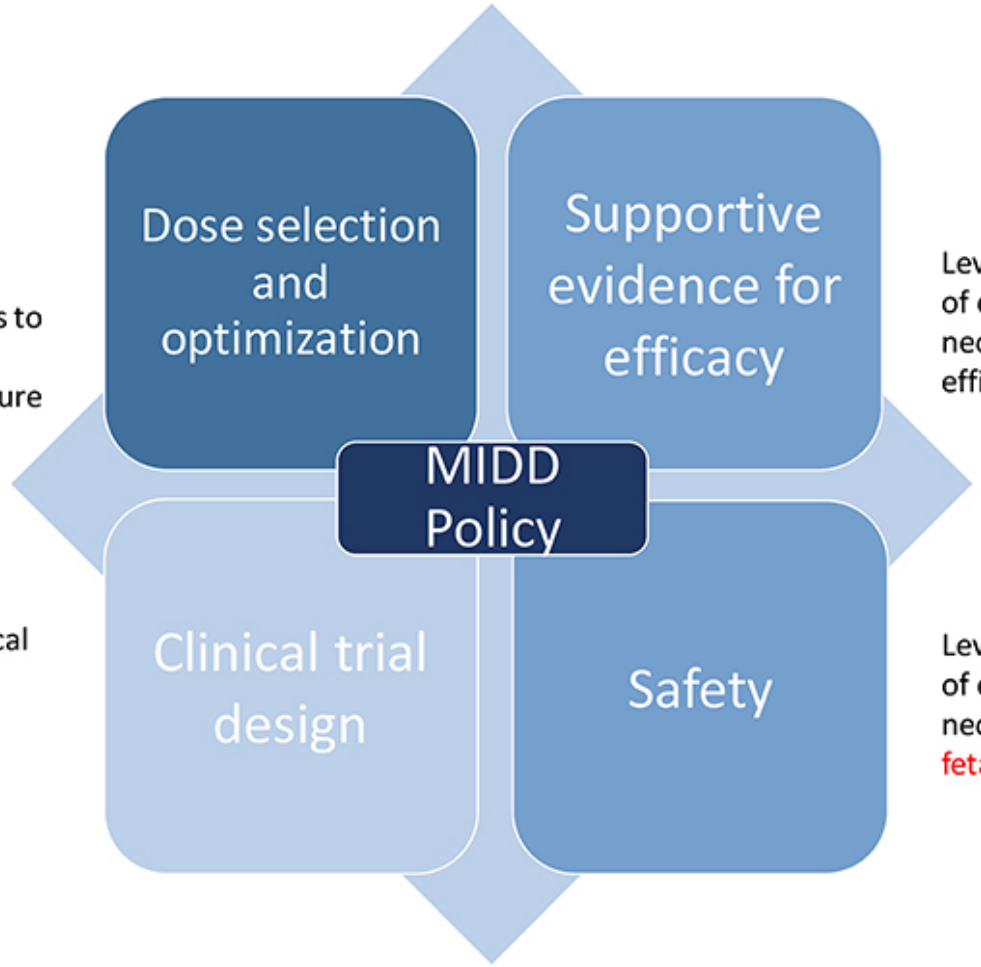
Table 2. Summary of recommendations on sampling strategies for pregnancy PK studies

Type of sampling	Method of analysis	Number of sampling points and participants[a]	Trimester to sample
Intensive PK samples	Noncompartmental analysis (NCA)	Usually 7–12 samples over one dosing interval at steady state from 12–24 participants	Preferably first, second, and third; or second and third; or early third (28–32 weeks of gestation) plus sparse sampling at early visits.
Sparse samples	Nonlinear mixed effects (NLME) modeling	Randomly assign participants to sampling windows; or Patients randomly contribute two or more samples to cover dosing interval; or Most patients contribute one sample at a specified timepoint.	

We can do better than this!

Clin Pharma and Therapeutics, Volume: 110, Issue: 1, Pages: 36-48, First published: 15 September 2020, DOI: (10.1002/cpt.2048)

Leverage available PK data in nonpregnant patients/animal studies to optimize dosing in pregnancy using exposure matching



Leverage prior knowledge of exposure-response in neonates for in-utero efficacy

Inform pregnancy clinical trial design using prior knowledge (PBPK, PK, disease modeling) and clinical trial simulation

Leverage prior knowledge of exposure-response in neonatal exposure for fetal safety

INTERPRETATION

Physiological changes and potential impact on PK of drugs.

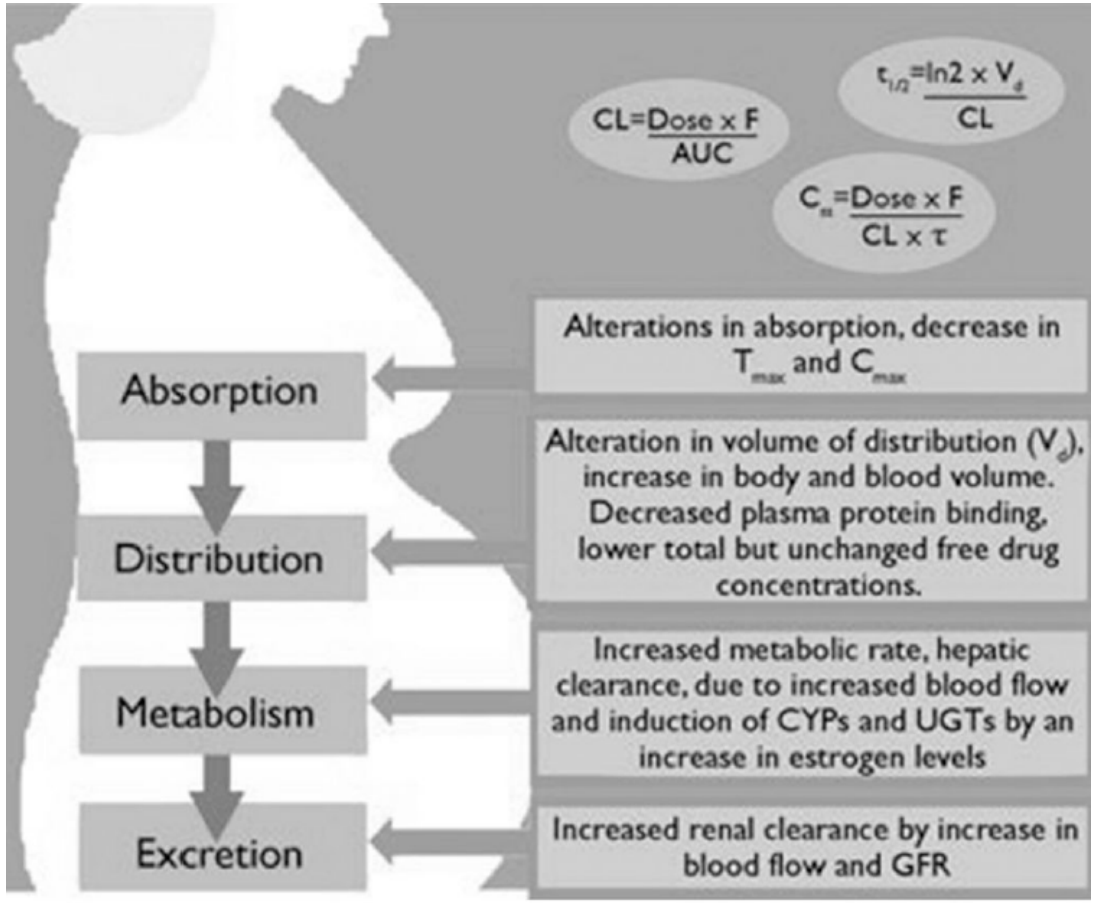
Pharmacokinetic parameter	Effect of pregnancy	Potential impact on pharmacokinetics	Clinical example
Absorption	Decrease in gastrointestinal motility and gastric emptying time Increase in gastric pH Increase in gastrointestinal blood flow Alterations in enzymes and transporters involved in absorption of drugs	Increase or decrease in the rate of absorption Increase or decrease in bioavailability	Aspirin C_{max} decreased by 29% during pregnancy (4) Lower C_{max} of metoprolol during pregnancy (5)
Distribution	Increase in cardiac output Increase in total body water and fat Decrease in plasma protein binding	Increase in volume of distribution	Increase in volume of distribution of metoprolol during pregnancy (5)
Metabolism	Alterations of CYP and UGT enzyme activity Increase in hepatic blood flow	Increase or decrease in metabolism of substrates	Decrease in clearance of caffeine (CYP1A2 substrate) during pregnancy (6) Increase in Clearance of lamotrigine (UGT1A4 substrate) during pregnancy as compared to postpartum (7)
Excretion	Increase in renal blood flow Increase in glomerular filtration rate Alterations of enzymes and transporters involved in tubular reabsorption and secretion	Increase in renal excretion Increase or decrease in tubular reabsorption and secretion	Unbound renal secretion of digoxin increased during pregnancy due to increased P-gP activity (8) Increased renal secretion and renal clearance of amoxicillin during pregnancy as compared to postpartum (9)

TOOLS AND APPROACHES: GENERAL CONSIDERATIONS

- Over the past several years, there has been an increase in the application of modeling and simulation approaches such as population PK (PopPK) and physiologically based PK (PBPK) modeling to provide guidance on drug dosing in those special patient populations.
- Population PK models rely on measured PK data, whereas physiologically based PK models incorporate physiological, preclinical, and clinical data into the model to predict drug exposure during pregnancy.
- These modeling strategies offer a promising approach to identify the drugs with PK changes during pregnancy to guide dose optimization in pregnancy, when there is lack of clinical data.

Chaphekar N, Dodeja P, Shaik IH, Caritis S, Venkataramanan R. Maternal-Fetal Pharmacology of Drugs: A Review of Current Status of the Application of Physiologically Based Pharmacokinetic Models. Front Pediatr. 2021 Nov 3;9:733823. doi: 10.3389/fped.2021.733823. PMID: 34805038; PMCID: PMC8596611.

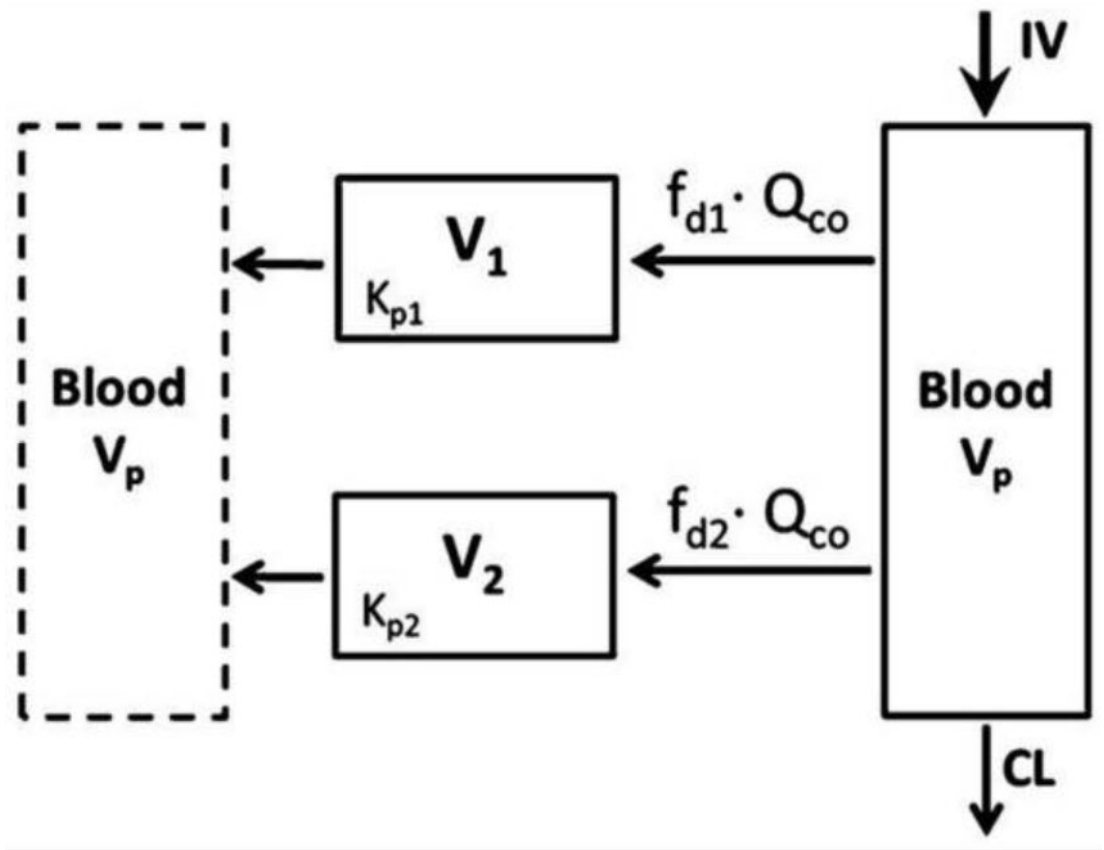
TOOLS AND APPROACHES: POP-PK APPROACH



- "There are several available approaches to studying pharmacokinetic changes in pregnancy."
- "Single trough screening studies can provide qualitative estimates of elimination clearance, which with the dosing rate determines the steady-state drug concentration, throughout pregnancy and into the postpartum period."
- "Population pharmacokinetic studies such as two stage pharmacokinetic studies and studies using a nonlinear mixed effects pharmacokinetic modeling approach can characterize pharmacokinetic changes more rigorously."

Avram MJ. Pharmacokinetic studies in pregnancy. Semin Perinatol. 2020 Apr;44(3):151227. doi: 10.1016/j.semperi.2020.151227. Epub 2020 Jan 27. PMID: 32093881; PMCID: PMC7323629.

TOOLS AND APPROACHES: POP-PK APPROACH



- **Requires a simplified model structure of non-physiologic parameters which approximate the "pregnant state"**
- **Still often referred to as a minimal PBPK model**
  - Fewer parameters
  - Difficult to capture time-based changes in underlying physiology
  - Fetus as a compartment?

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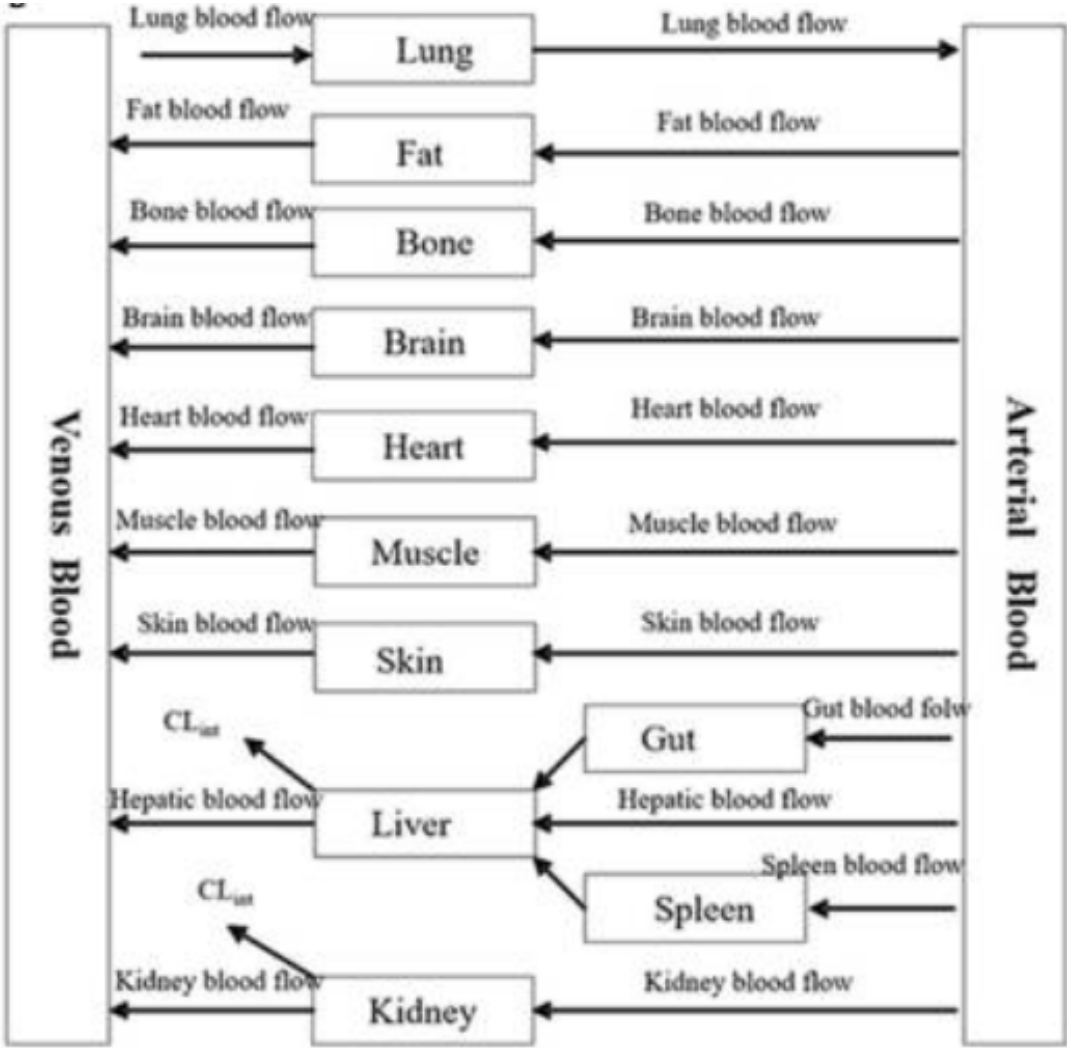
TOOLS AND APPROACHES: PBPK APPROACH



- **Physiologic representation of relevant actual parameters which an be verified against actual physiologic data**
- **Model reduction possible as appropriate / required**
  - Physiologic parameters
  - Time-based changes in underlying physiology captured
  - Fetus as its own model structure

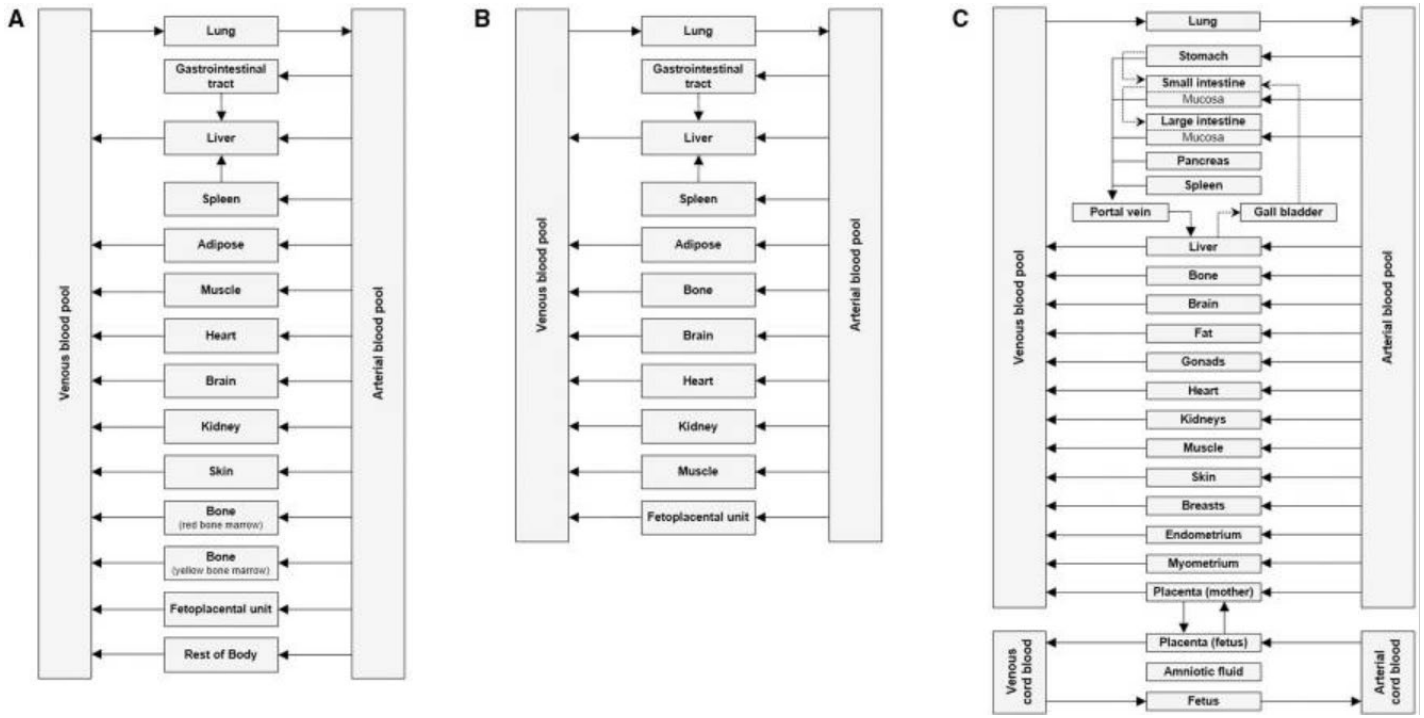
Chaphekar N, Dodeja P, Shaik IH, Caritis S, Venkataramanan R. Maternal-Fetal Pharmacology of Drugs: A Review of Current Status of the Application of Physiologically Based Pharmacokinetic Models. Front Pediatr. 2021 Nov 3;9:733823. doi: 10.3389/fped.2021.733823. PMID: 34805038; PMCID: PMC8596611.

TOOLS AND APPROACHES: PBPK APPROACH

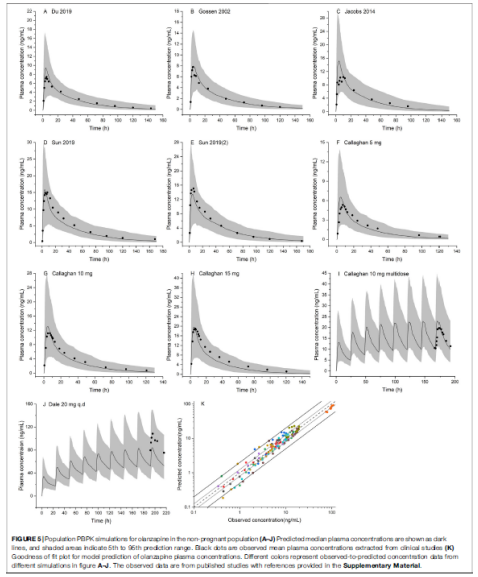
- **Physiological parameters that are modified for pregnancy prediction in Simcyp p-PBPK model.**

List of parameters
Cardiac output
Total body weight
Total fat
Plasma volume
Red blood cell volume
Hematocrit
Serum albumin
Skin blood flow rate
Adipose blood flow rate
Renal blood flow rate
Fetoplacental unit blood flow rate
Enzyme and transporter activity

Basic structure of p-PBPK model in (A) Gatsroplus (B) SimCyp and (C) Open Systems Pharmacology



TOOLS AND APPROACHES: PBPK APPROACH IN PRACTICE



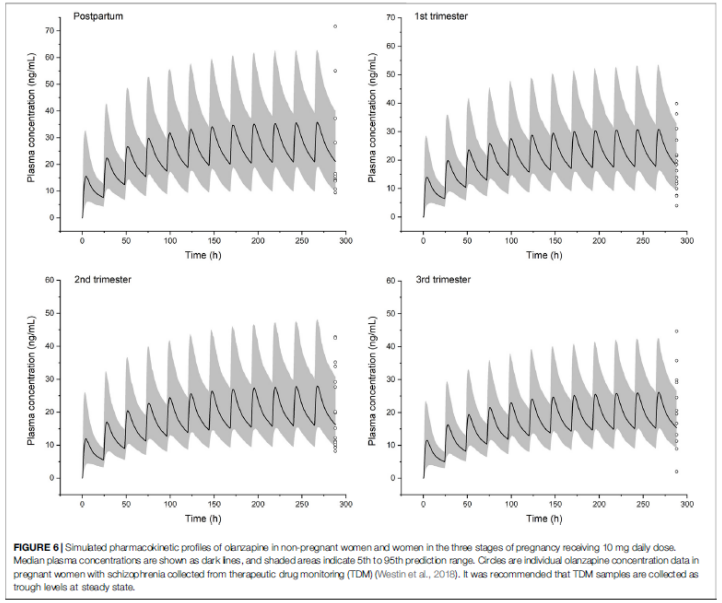
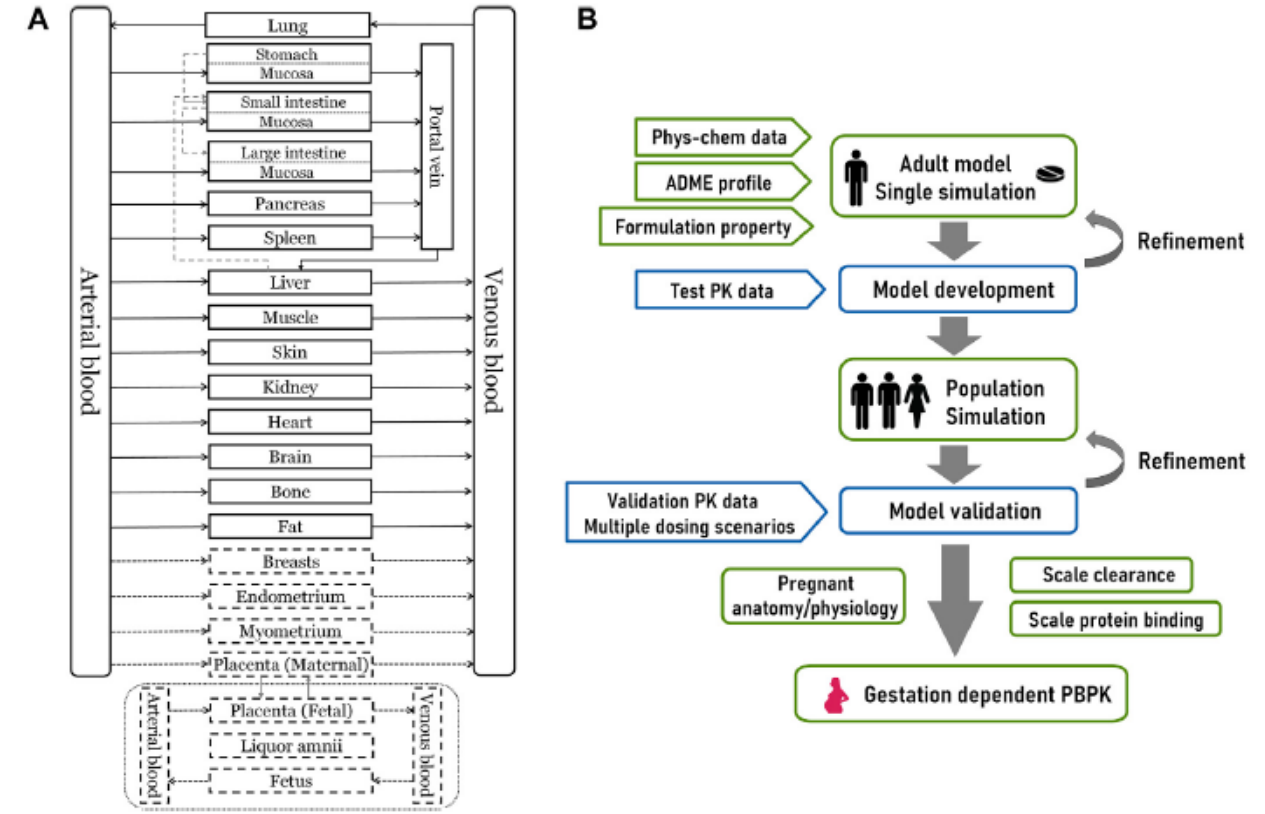


FIGURE 6 | Simulated pharmacokinetic profiles of olanzapine in non-pregnant women and women in the three stages of pregnancy receiving 10 mg daily dose. Median plasma concentrations are shown as dark lines, and shaded areas indicate 5th to 95th prediction range. Circles are individual olanzapine concentration data in pregnant women with schizophrenia collected from therapeutic drug monitoring (TDM) (Westin et al., 2018). It was recommended that TDM samples are collected as trough levels at steady state.

Olanzapin example (A) A 27-compartment physiological model of pregnant women in Mobi®. The dotted portion is nine gestation-specific compartments (B) The schematic diagram for PBPK modeling workflow. Phys-chem, physicochemical; ADME, absorption, distribution, metabolism, and excretion.



- Recent PBPK examples demonstrate excellent performance with respect to historical PK trials
- Simulations across trimesters are compelling and consistent with expectations but need to be challenged with data in the future.

TOOLS AND APPROACHES: FUTURE CONSIDERATIONS

Maternal pharmacology	Fetal pharmacology
1. Lack of data on time course of changes in expression and activities of various phase 1 and 2 enzymes during pregnancy and postpartum	1. Actual fetal exposure / blood and tissue concentration prediction not available—need for validation with meaningful clinical data
2. Lack of data on Time course of changes in various transporters during pregnancy and postpartum	2. Lack of data on exposure response relationship in fetus
3. Lack of data from same person during and post-delivery	3. Placental enzymes and transporter expression data to incorporate transplacental transfer in PBPK model
4. Lack of PD measures—Relationship between exposure and response	4. Maternal-placental-fetal drug partitioning—factors impacting this such as plasma protein binding in mother, fetus, and role of placental transporters
5. Lack of information on potential impact of other comorbid conditions on PK/PD	
6. Lack of PBPK models of biologics	

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REPORT CARD:

HOW HAS THE MODELING PERFORMED THUS FAR?

- **> 40 drugs analyzed via PBPK M&S to aid the design, analysis and dosing recommendations for pregnant women**
- **PK, PGx and some biomarker data available for analysis**
- **Various routes of administration accommodated**
- **Various model constructs and software solutions utilized**
  - Various dosing scenarios across gestational age often evaluated
  - Comparison to non-pregnant state a common comparator
  - Strong emphasis on providing dosing guidance and recommendations
  - Some focus on study designs and sampling considerations.
- **Performance against measure observations (when available) was excellent**

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REPORT CARD:

HOW HAS THE MODELING PERFORMED THUS FAR?

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TABLE 5 | Review of published p-PBPK models.

Compound	Route of administration	Clinical observations	Recommended dose adjustment based on PBPK modeling	Software	Referen
Acetaminophen	IV and oral dosing	Lower acetaminophen concentrations during pregnancy as compared to non-pregnant women	No dose adjustments since there is lack of data on toxicity of the metabolite NAPQI	Open Systems Pharmacology®	(29)
Amoxicillin	IV bolus and infusion	Increased renal clearance during pregnancy and postpartum	May need increased dosing No clinical recommendations	Open Systems Pharmacology®	(30)
Betamethasone	IV, IM and oral dosing	Increased clearance during pregnancy	No clinical recommendations	Simcyp®	(31)
Buprenorphine	Sublingual	Decreased buprenorphine exposure during pregnancy as compared to postpartum	Increased dose/ more frequent dosing	Simcyp	(32)
Caffeine	Oral dosing	Increased maternal and fetal exposure during pregnancy due to reduced CYP1A2 activity	Limit caffeine intake	GastroPlus®	(33)
Caffeine, Midazolam, Nifedipine, Metoprolol Ondansetron, Granisetron, Diazepam and Metronidazole	IV and oral dosing	Increase in clearance of CYP2A6, CYP2E1, CYP2D6 and CYP3A4 substrates and decreased clearance of CYP1A2 and CYP2C19 substrates	Likely changes in dosing No clinical recommendations	Open Systems Pharmacology®	(34)
Caffeine, Metoprolol, Midazolam	IV Bolus, Oral dosing	100% increase, 30% decrease and a 35% decrease in the exposure of caffeine, metoprolol, and midazolam respectively during pregnancy	Decreased dose for caffeine and increased dose for metoprolol and midazolam	Simcyp®	(35)
Cefazolin, Cefuroxime, Cefradine	IV and oral dosing	Increased clearance of the three drugs during pregnancy	Increased dose during pregnancy	Open Systems Pharmacology®	(36)
Ceftazidime, Cefuroxime,	IV and Oral dosing	Decrease of *in vivo* drug exposure (for all 6 drugs) in	No dose changes	Simcyp®	(37)

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THANK YOU

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