# Maternal-Fetal PBPK Modeling of Antipsychotic Drugs as Case Study

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# Disclaimer

This presentation is the opinion of the author only and does not represent FDA policy and regulation

# Perinatal Health and Regulatory Need

- Need for computational alternatives to support the evaluation of safety and efficacy of therapeutic agents for patients in perinatal life-stages who are frequently excluded from clinical trials
- Utilize life-stage PBPK models as tools to evaluate and optimize treatments specifically in the perinatal life-stages
- The confidence in the use of such tools in regulatory decision-making and pose challenges in conducting timely and thorough review of submissions

# Project Goal and Purpose

- To develop a PBPK model for different perinatal life stages (fetuses, neonates, infants, young children, pregnant and lactating women)

- To serve as an in-house tool allowing for flexibility to conduct any investigative analysis, and to better inform dosing for antipsychotics and COVID-19 treatments in these data-sparse populations

# Strategy for Model Development

**Curate data:** Gather available information (existing databases, body of literature, and FDA in-house data) for parameterization of perinatal life-stage PBPK models

**Design model:**

- Maternal Component
- Fetal Component
- Population Modeling
- Other Perinatal Life-stages including Pediatrics

**Code model component:** Code the model using an open-source language based on the determined model structure and parameters. Conduct sensitivity analysis to confirm model dimensionality

**Test model component:** Verify the model's predictive capability using case studies

**Document model and scope gap/needs:** Document model code including assumptions and decisions. Identify gaps in data and modeling needs to guide future research to facilitate regulatory application of PBPK modeling tools in perinatal periods

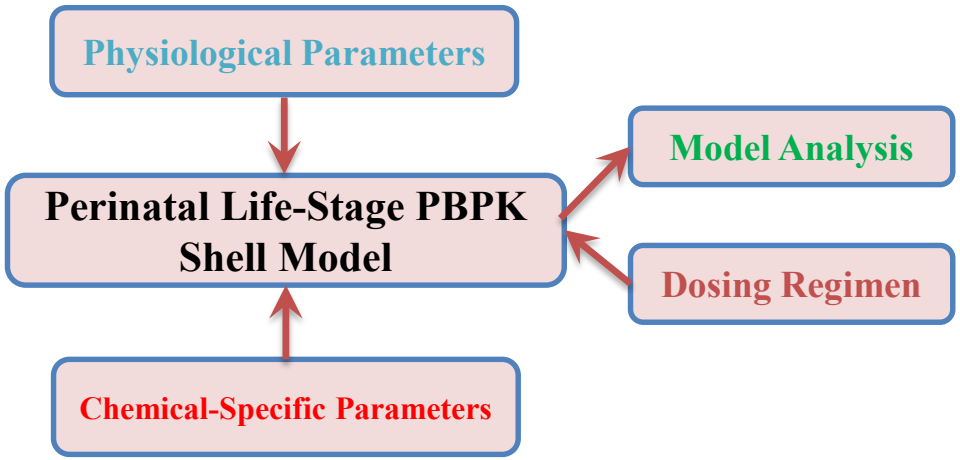
# Repository for Physiological Changes

## Equations for Maternal Fetal Physiological Changes

| Parameters | Abduljalil et al. 2012 & 2019 | Dallmann et al. 2017 | Kapraun et al. 2019 |
|---|---|---|---|
| **Total Body Fat (kg)** | 17.14+0.1305*GA+0.0008*GA^2 (Eq 9) | 20.2+0.125*FA (Eq 15) | 17.067+0.14937*GA (Eq 3) |
| **Cardiac Output (L/h)** | 301+5.916*GA-0.088*GA^2 (Eq 14) | 6.09exp(-exp(-0.352logFA + 1.36)) + 5.14 (Eq 19 **L/min**) | 301.78+3.2512*GA+0.15947*GA^2-0.0047059*GA^3 (Eq 13) |
| **Plasma Volume (L)** | 2.50-0.0223*GA+0.0042*GA^2-0.00007*GA^3 (Eq 15) | 2.36+0.0000841*FA+0.00395*FA^2-0.0000817*FA^3 (Eq 29) | 2.4958+1.2406/(1+exp(-0.31338*(GA-17.813))) (Eq 5) |
| **Hematocrit (%)** | 39.1-0.0544*GA-0.0021*GA^2 (Eq 17) | 40.1+0.0299*FA-0.0180*FA^2+0.000401*FA^3 (Eq 21) | 39.192-0.10562*GA -(7.1045* 10^-4)*GA^2 (Eq 24) |
| **Albumin (g/L)** | 45.8-0.1775*GA-0.0033*GA^2 (Eq 19) | 14.7*exp(-0.0454*FA)+31.7 (Eq 9) | NA |
| **Alpha-1-Acid Glycoprotein AAG (g/L)** | 0.74-0.0088*GA+0.0001*GA^2 (Eq 20) | 0.0000768*FA^2-0.00573*FA+0.701 (Eq 11) | NA |
| **Glomerular Filtration Rate** | 114+3.2367*GA-0.0572*GA^2 (mL/min, Eq 27) | 0.113+8.73*FA-0.716*FA^2+0.0245*FA^3-0.000294*FA^4 (FA<=14)<br>0.15 (FA>=14) (L/min, Eq 27) | (17+(12.5-17)/40*GA)/100 (unitless, Eq 16) |
| **Placenta Volume** | 0-0.716*GA+0.9149*GA^2-0.0122*GA^3 (mL, Eq 43) | 0.937*exp(-6.10*exp(-0.0813*FA))-0.00211 (L, Eq 48) | 0-1.7646*GA+0.91775*GA^2- 0.011543*GA^3 (mL, Eq 8) |
| **Amniotic Fluid Volume** | 1.9648*GA-1.2056*GA^2+0.2064*GA^3-0.0061*GA^4-0.00005*GA^5 (mL, Eq 44) | exp(-10+1.22*GA-0.0653*GA^2+0.00169*GA^3-0.0000169*GA^4) (L, Eq 33) | 822.34/(1+exp(-0.26988*(GA-20.150))) (mL, Eq 9) |
| **Fetal Tissue Volume** | 0.01*exp((0.955/0.0702)*(1-exp(-0.0702*GA))) (mL, Eq 42) | 5.90/(1+exp(-4.45*logFA + 15.8)) (L, Eq 39) | NA |

Abduljalil et al. 2012 (PMID: 22515555); Abduljalil et al. 2019 (PMID: 29987449); Dallmann et al. 2017 (PMID: 28401479); Kapraun et al. 2019 (PMID: 31048866); Zhang et al. 2017 (PMID: 28588050)

# Code the Pregnancy PBPK Model in R




**Model Transparency:** open-source R language ("mrgsolve")

## Shell Model (generic base model)

```
//change of fraction unbound in plasma
double fup = fup_0*(1+Kaff*AAG_0)/(1+Kaff*AAG);

//liver clearance
double CL_Li = ((VmaxH/KmH)*MPPGL*Vli*1000*60*1e-6)/fumic*Activity_CYP3A4;

[ODE]
//Calculation of tissue drug concentrations (mg/L)
double Cblood = BLOOD/Vbl;
double Cadipose = ADIPOSE/Vad;
double Ckidney = KIDNEY/Vki;
//double CgutLumen = GUTLUMEN/VguLumen;
double Cgut = GUT/VguWall;
double Crichly = RICHLY/Vrp;
double Cpoorly = POORLY/Vpp;
double Cliver = LIVER/Vli;
double Cpfu = PFU/(Vpfu+1-PF);

//capilary blood concentration
double Cvad = Cadipose/Kpad*BP;
double Cvgu = Cgut/Kpgu*BP;
double Cvki = Ckidney/Kpki*BP;
double Cvrp = Crichly/Kprp*BP;
double Cvpp = Cpoorly/Kppp*BP;
double Cvli = Cliver/Kpli*BP;
double Cvpfu = Cpfu/Kppfu*BP;
double Cven = (Qad*Cvad + Qki*Cvki + Qrp*Cvrp + Qpp*Cvpp + Qli*Cvli + Qpfu*Cvpfu)/QC;

//ODEs
dxdt_GUTLUMEN = -(ka+ki)*GUTLUMEN;
dxdt_GUT = ka*GUTLUMEN + QguWall*(Cblood - CVgu);
dxdt_ADIPOSE = Qad*(Cblood - CVad);
dxdt_KIDNEY = Qki*(Cblood - CVki) - CL_Ki*(fup*CVki);
dxdt_RICHLY = Qrp*(Cblood - CVrp);
dxdt_POORLY = Qpp*(Cblood - CVpp);
dxdt_LIVER = QguWall*CVgu + (Qli-QguWall)*Cblood - Qli*CVli - CL_Li*(fup*CVli);
dxdt_PFU = Qpfu*(Cblood - CVpfu);
dxdt_CL = CL_Ki*(fup*CVki) + CL_Li*(fup*CVli);
dxdt_BLOOD = QC*(Cven-Cblood);
dxdt_ABS = ka*GUTLUMEN;

double massbalance = BLOOD+ADIPOSE+KIDNEY+GUT+RICHLY+POORLY+LIVER+PFU+CL-ABS;
double SumQ = (Qad + Qli + Qki + Qpfu + Qrp + Qpp)/QC;
double SumV = (Vbl + Vad + VguWall + Vli + Vki + Vpfu + Vrp + Vpp)/BW;
```

### 1. Read Shell Model + Source the Equations

```
library(tibble)
library(tidyverse)
library(magrittr)

setwd("C:/pPBPK/shell model/Darunavir")
source("../equations for physiological parameters.R")
darunavir_oral_600 <- read_excel("./Darunavir_oral_600.xlsx") %>% as.data.frame()
mod <- mread_cache("Darunavir")
param(mod)
```

### 2. Generate Physiological Parameters

```
pPBPK_para <- tibble(ID = rep(1:N, each = end/delta+1),
                     GA = rep(seq(GA_0, GA_0+(N-1)*10, 10), each = end/delta+1),
                     timeH = rep(time_seq, times = N)) %>%
  mutate(GABW = GA + (timeH/7/24)) %>% # AGE2
  mutate(BW = BW_A(GABW)) %>%
  mutate(QCC = QC_D(GA_to_FA(GABW))/BW^0.75) %>%
  mutate(Vbrc = Vbrc_K, VguWallc = VguWallc_K, Vlic = Vlic_K, Vskc = Vskc_D, Vthc = Vthc_K) %>%
  mutate(Vadc =vad_D(GA_to_FA(GABW))/BW, Vblc = Vplasma_to_Vblood(Vplasma_D(GA_to_FA(GABW)), HCT_D(GA_to_FA(GABW)))/BW,
         Vbrec = Vbre_D(GA_to_FA(GABW))/BW, Vhec = Vhe_D(GA_to_FA(GABW))/BW, Vkic = Vki_D(GA_to_FA(GABW))/BW,
         Vpfuc = (Vpl_D(GA_to_FA(GABW))+Vfl_D(GA_to_FA(GABW))+Vaf_D(GA_to_FA(GABW)))/BW,
         Vutc = Vut_D(GA_to_FA(GABW))/BW) %>%
  mutate(Qadc = QadC_D, Qhec = Qhec_D) %>%
  mutate(Qbrec = Qbrec_D(GA_to_FA(GABW)), QguWallc = QguWallC_K(GABW), Qlic = Qlic_K(GABW), Qthc = QthC_K(GABW),
         Qskc = QskC_D(GA_to_FA(GABW))) %>%
  mutate(Qkic =Qki_D(GA_to_FA(GABW), HCT_D(GA_to_FA(GABW)))/(QCC*BW),  Qutc = Qut_D(GA_to_FA(GABW))/(QCC*BW),
         Qpfuc = (Qpl_D(GA_to_FA(GABW))+Qfl_D(GA_to_FA(GABW))+Qut_D(GA_to_FA(GABW)))/(QCC*BW),
         Qbrc = Qbr_D(GA_to_FA(GABW))*Vbrc/QCC) %>%
  mutate(Activity_CYP3A4 = Activity_CYP3A4_A(GABW)) %>%
  mutate(AAG = AAG_D(GABW)) %>%
  mutate(PF = rep(c(1), N*(end/delta+1)))
```

### 3. Set the Dosing Regimen + Run the Simulation

```
pPBPK_para %<>%
  mutate(EVID = if_else((timeH %% ii) == 0 & timeH <=addl*ii, true = 1, false = 0)) %>%
  mutate(AMT = case_when(EVID == 1 ~ 600)) %>%
  mutate(CMT = if_else(EVID == 1, true = 1, false = 2)) %>%
  mutate(TIME = timeH)

simulation <- mod %>% mrgsim_d(data=pPBPK_para) %>% as.data.frame() %>% slice(3:n())
```

# Pregnancy PBPK Model

## Abduljalil et al. 2012

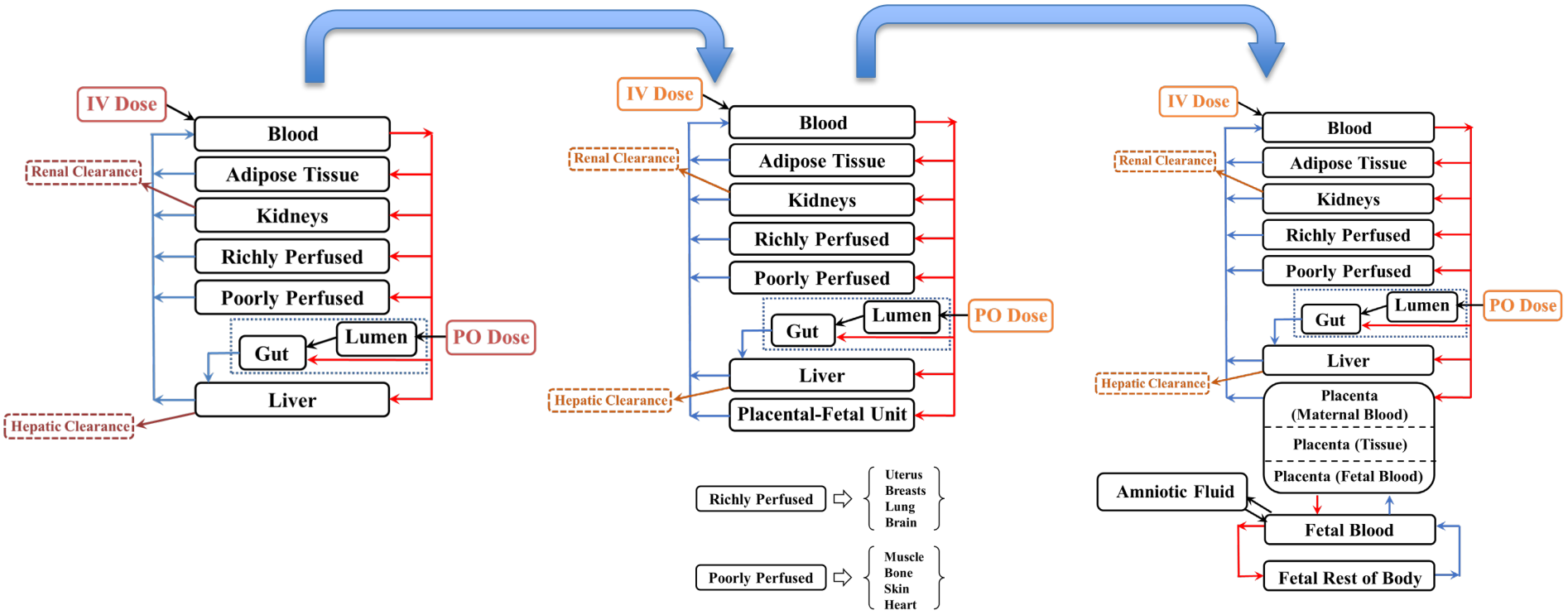
BW = 61.1+0.2409×GA+0.0038×GA^2
CO = 301 + 5.916×GA -0.088×GA^2
……

## Dallmann et al. 2017

CO = 6.09*exp(-exp(-0.352*lg(FA) + 1.36)) +5.14
HCT = 40.1+0.0299*FA-0.0180*FA^2+0.000401*FA^3
……

## Customized Equations

BW = 61.103-0.010614*GA+0.029161*GA^2-(5.0203*10^-4)*GA^3
CO = 301.78 + 3.2512*GA+0.15947*GA^2-0.0047059*GA^3
……




**Non-Pregnant Adult Model** → **Pregnancy Model** → **Maternal-Fetal Model**



BW: body weight; CO: cardiac output; HCT: hematocrit; GA: gestational age; FA: fertilization age

# Application of the Model to Antipsychotic Drugs

- Antipsychotics are widely used during pregnancy and sometimes for the pre-existing condition
- Antipsychotics are often off-label use for pregnant women
- Antipsychotics are being prescribed increasingly during pregnancy and the postpartum period
- The dose-dependent drug effects and toxicity of antipsychotics on fetuses are still lacking
- Concerns and debates for birth defects using of antipsychotics during the first trimester
  - Aripiprazole: High Protein Binding; Multiple Metabolic Enzymes (with more than one metabolites)
  - Risperidone: High Protein Binding; Multiple Metabolic Enzymes
  - Clozapine: High Protein Binding; Multiple Metabolic Enzymes

# Application of the Model to Antipsychotic Drugs

| Drugs | Human fup | logP | MW | pKa | Kp | Metabolism | BDDCS | ECCS | Available PBPK | Available pregnancy PBPK | Available pregnancy PK data |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Aripiprazole** | 0.01 | 5.21 | 448.4 | 7.6 | All Tissue to Plasma Partition Coefficients were Calculated using Rodgers and Rowland Method in Simcyp | CYP3A4<br>CYP2D6 | 2 | 2 | Yes<br>(Vieira et al. 2014) | No | Yes |
| **Risperidone** | 0.1 | 4.07 | 410.5 | 8.2 | | CYP2D6 (major)<br>CYP3A4 (minor) | 1 | 2 | Yes<br>(Kneller et al. 2020) | No | Yes |
| **Clozapine** | 0.05 | 3.21 | 326.8 | 7.5 | | CYP1A2<br>CYP2D6<br>CYP3A4 | 2 | 2 | Yes<br>(Wong et al. 2019) | No | Yes |

**Data Available for Non-Pregnancy Model**

**Available adult PBPK models**
**Aripiprazole**: Vieira et al. 2014 (PMID: 24556783)
**Risperidone**: Kneller et al. 2020 (PMID: 31359271)
**Clozapine**: Wong et al. 2019 (PMID: 30676661)

**Data Available for Pregnancy Model**

**Available PK data for non-pregnant adults and pregnancy**
**Aripiprazole**: Boulton et al. 2018 (PMID: 18563956); Westin et al. 2018 (PMID: 28643331)
**Risperidone**: Novalbos et al. 2010 (PMID: 20814331); Westin et al. 2018 (PMID: 28643331)
**Clozapine**: Hägg et al. 1999 (PMID: 10379638); Westin et al. 2018 (PMID: 28643331)

Values of physicochemical parameters are from DrugBank and PubChem



BDDCS: Biopharmaceutics Drug Disposition Classification System; ECCS: Extended Clearance Classification System

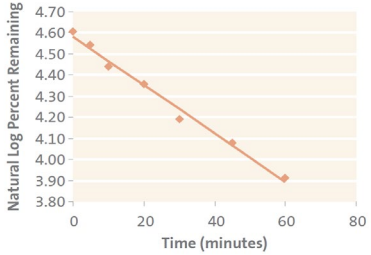
# *in vitro* to *in vivo* Extrapolation (IVIVE)

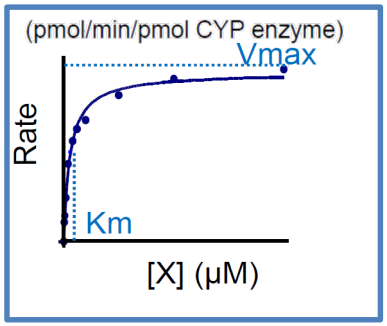
**Recombinant CYPs**

*In vitro* system

*In Vitro* $CLu_{int}$

µl / min / **per functional unit of system**




$$CL_{int,\ in\ vivo} = (CL_{int,\ in\ vitro}/FU_{mic}) \times ISEF \times MPPGL \times Abundance \times liver\ weight$$

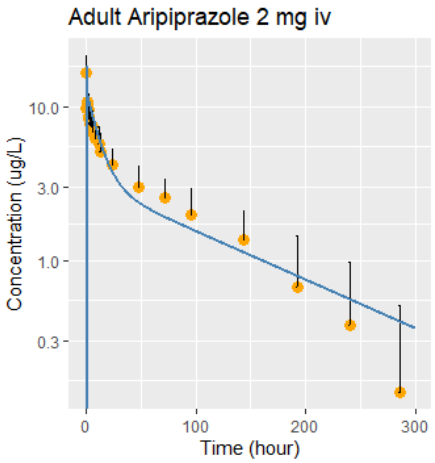
*In vitro to in vivo* extrapolation (IVIVE)

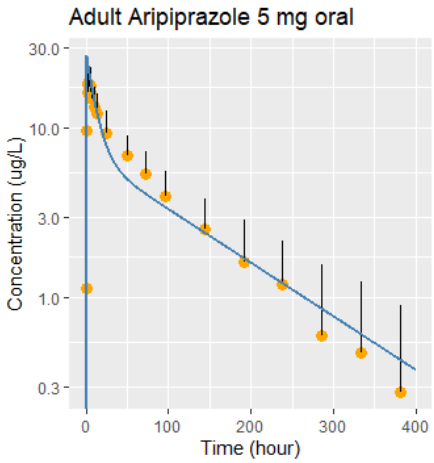
| Drugs | Metabolic Enzyme Isoforms | Metabolic Pathways | Vmax | Km | CLint (in vitro) | fumic: fraction unbound in microsomal systems (if available) | ISEF: Intersystem Extrapolation Factor (if recombinant enzymes used) | MPPGL: Microsomal Protein Per Gram of Liver (life-stage specific) | Total CLint (in vivo, per of kg liver) | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Unit | N/A | N/A | nmol/nmol P450/min | uM (pmol/µL) | µL/min/pmol | no units | unit less | mg/g | L/hr/kg | N/A |
| **Aripiprazole** | CYP2D6 | DM-1451 | 0.42 | 15.7 | 0.027 | 0.435 | 1.069 | 40 | 26.68 | FDA Review (2001) |
| | | DM-1452 | 3.92 | 27.9 | 0.141 | 0.435 | 1.069 | 40 | | |
| | | OPC-14857 | 2.81 | 26.2 | 0.107 | 0.435 | 1.069 | 40 | | |
| | CYP3A4 | DM-1451 | 12.5 | 514 | 0.024 | 0.435 | 0.226 | 40 | | |
| | | DM-1452 | 19.6 | 757 | 0.026 | 0.435 | 0.226 | 40 | | |
| | | OPC-14857 | 6.21 | 298 | 0.021 | 0.435 | 0.226 | 40 | | |
| **Rispiridone** | CYP2D6 | NA | NA | NA | 7.550 | 1 | 1 | 40 | 211.92 | Vieira et al. 2014 |
| | CYP3A4 | NA | NA | NA | 0.180 | 1 | 1 | 40 | | |
| **Clozapine** | CYP1A2 | NA | 13.1 | 14.2 | 0.923 | 1 | 0.571 | 40 | 81.12 | Ghoneim et al. 2020 |
| | CYP2D6 | NA | 4.5 | 19.5 | 0.231 | 1 | 1.069 | 40 | | |
| | CYP3A4 | NA | 11.6 | 91.6 | 0.127 | 1 | 0.226 | 40 | | |

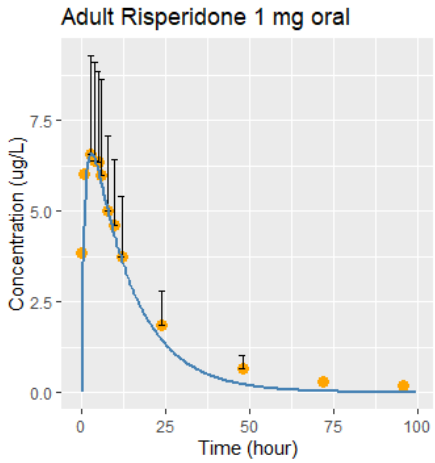
Proctor et al. 2004; Song et al. 2017

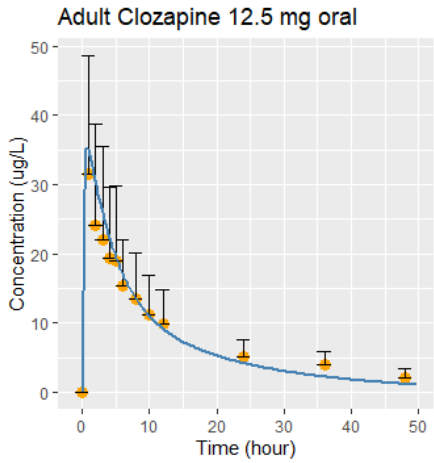
# Model Simulation

## Model Calibration with Non-pregnant Adults

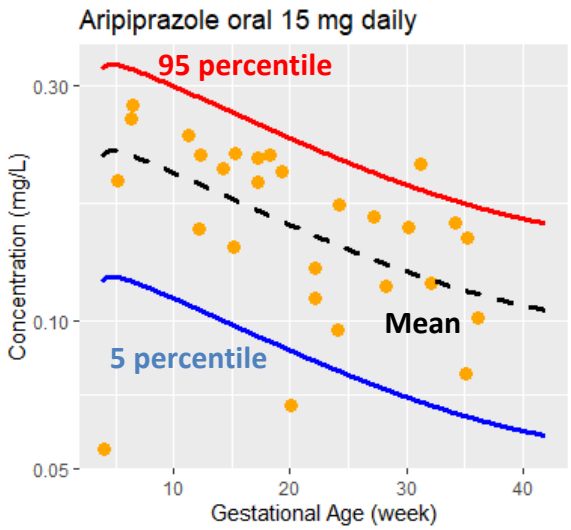


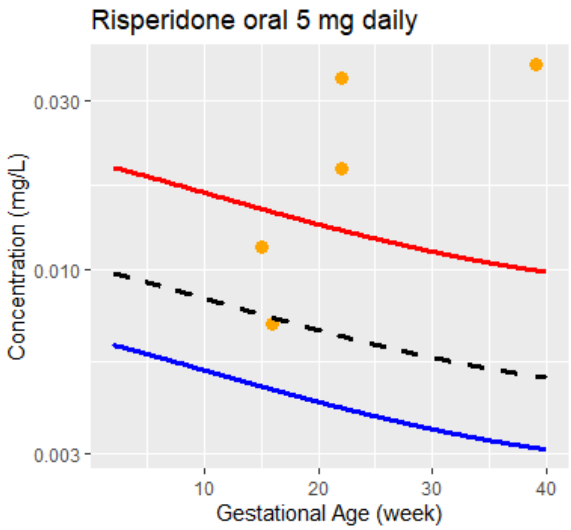



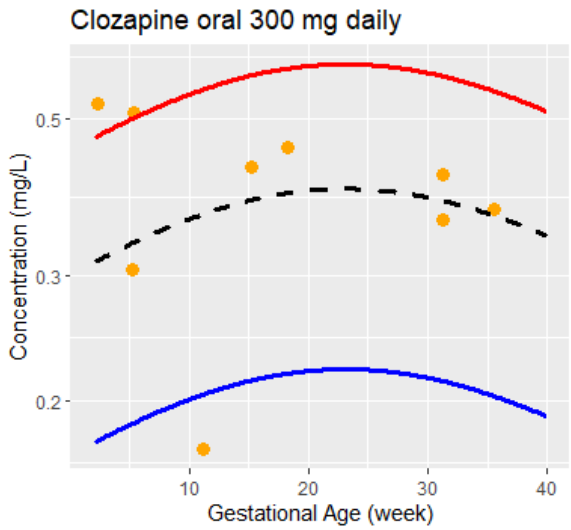




## Model Evaluation with Daily Dose through Pregnancy



# Pregnant Women Population

## Based on National Health and Nutrition Examination Survey (NHANES)

**Age**

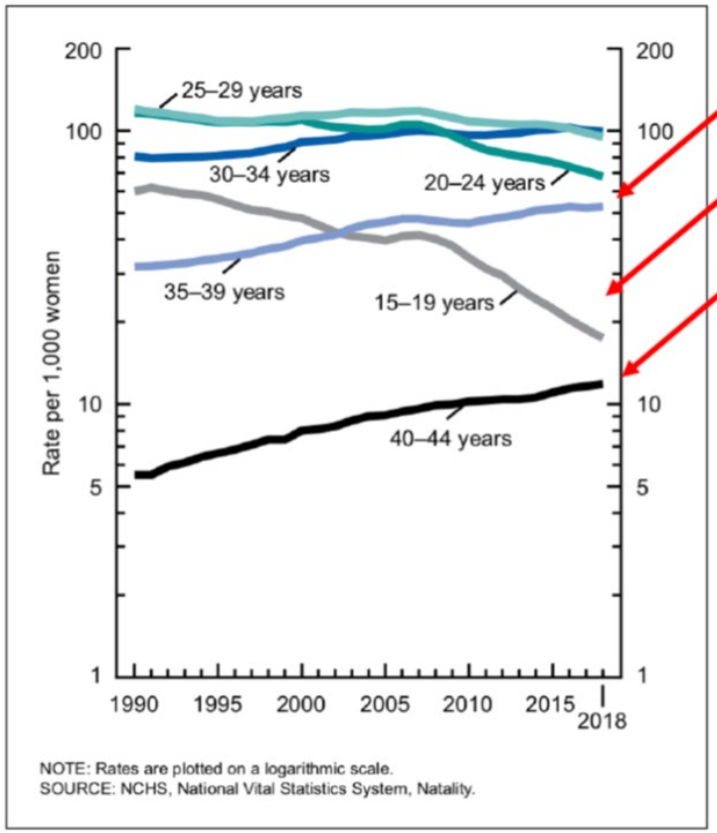
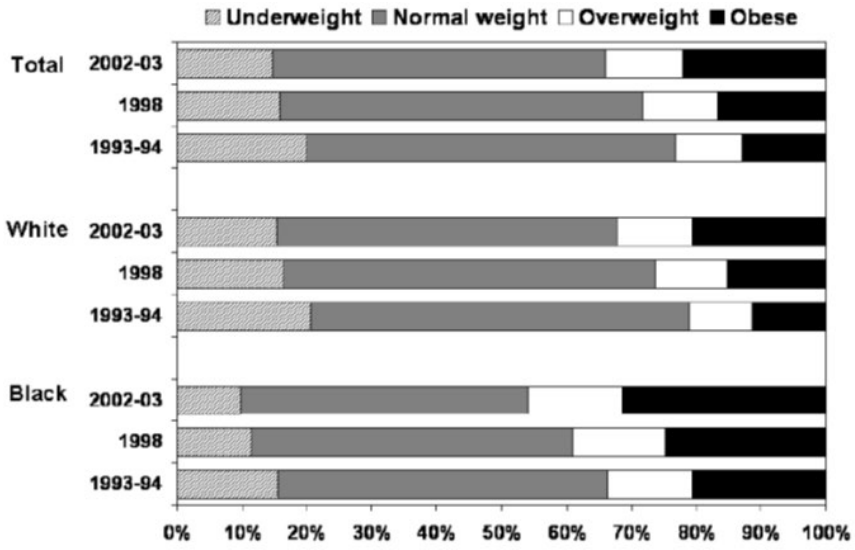



**Figure 3. Birth rates, by age of mother: United States, 1990–2018**

**CDC NVSS Report**

**Age ratios of pregnant women change throughout years**

**Ethnicity & BMI**



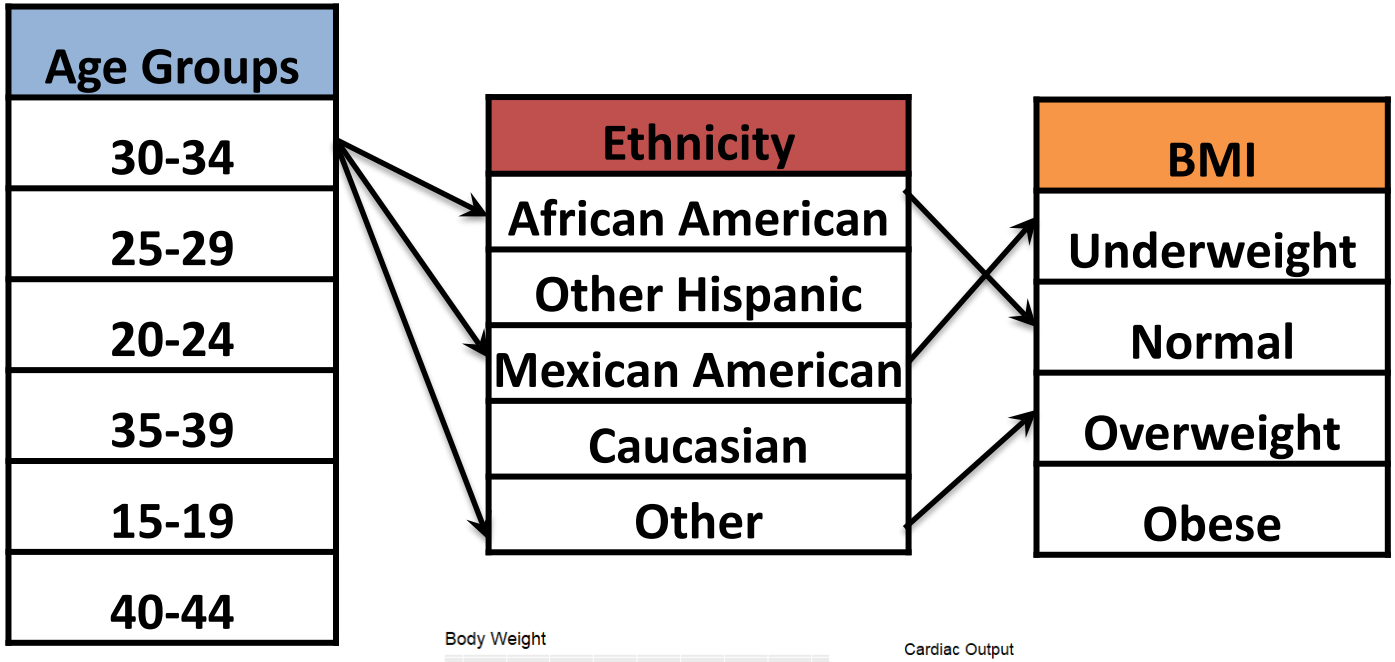

*1990 cut points. SOURCE: Kim et al., 2007. (IOM Report, 2009)

**IOM Report, 2009**

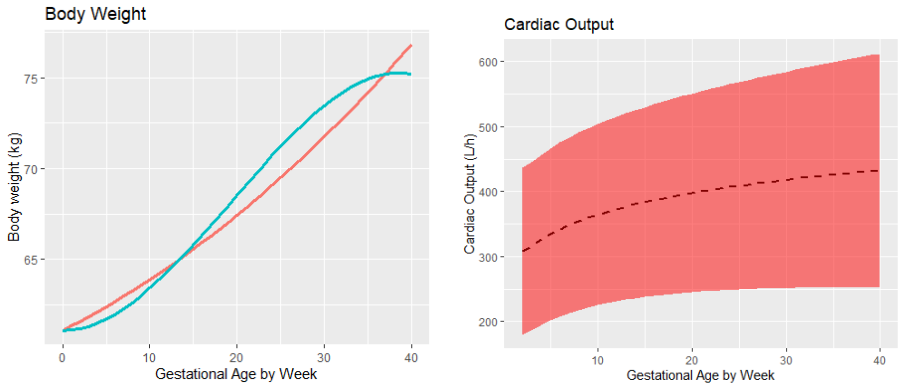
# Population Pregnancy Model

- Hierarchical Workflow (2 Steps)

1. **HTTK Population Generation**




2. ***Monte Carlo* Simulation**
   **Time dependent changes**
   **Dynamic Variability**

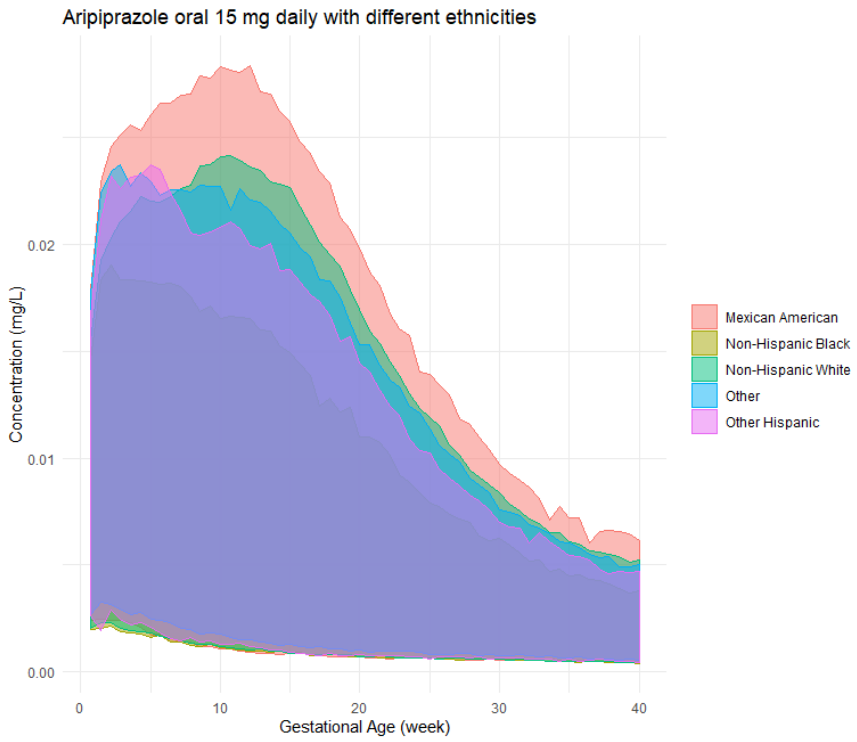


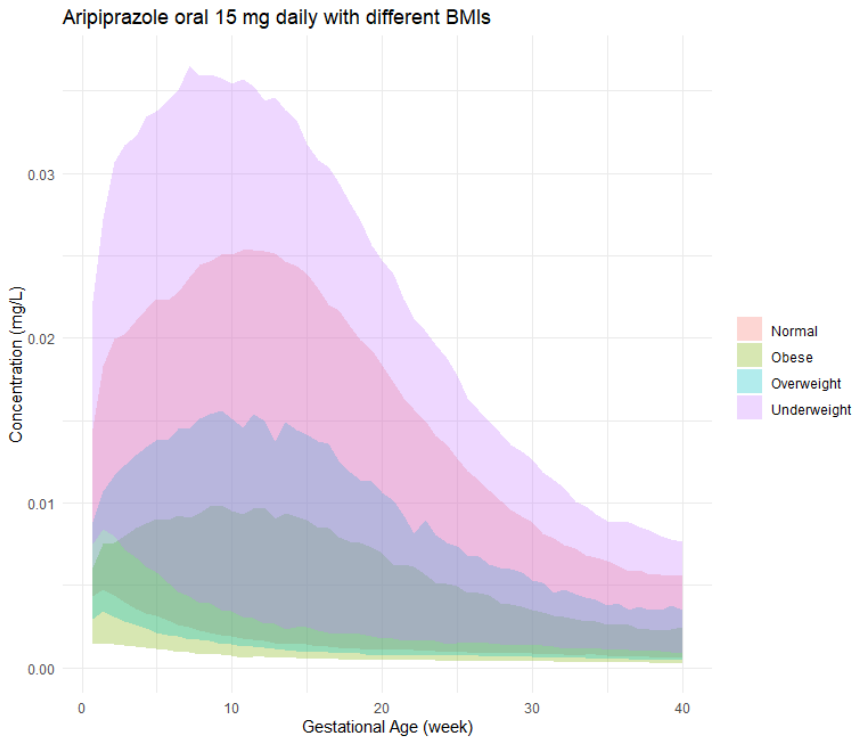



Abduljalil et al. 2012; Dallmann et al. 2017; Kapraun et al. 2019

# Pharmacokinetic Profiling

- By applying the population model based on different ethnic, BMI and age groups, the subgroups can be separated to view the PK profile individually

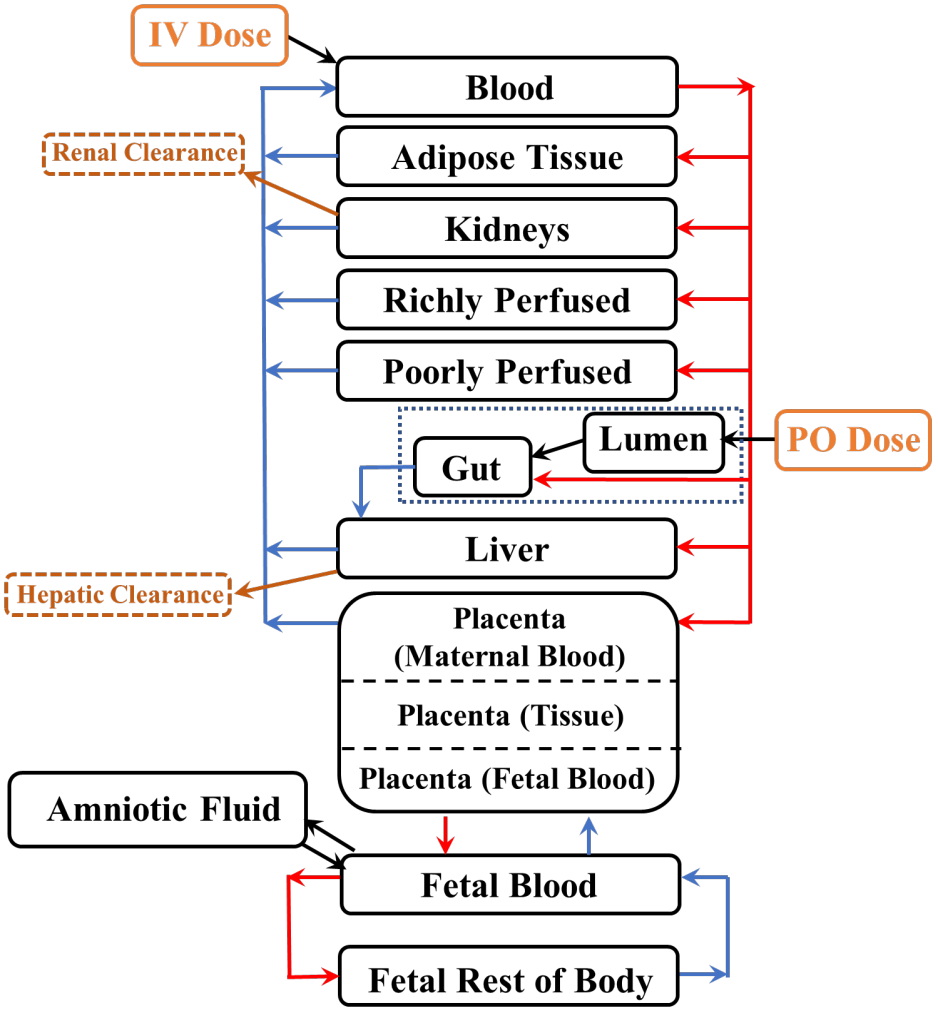


# Maternal-Fetal Model Simulation

## Model Assumptions:

1. **The placenta considered as a permeability-limited compartment.**
2. **The passive diffusion of drugs is proportional to the placenta villous surface area.**
3. **The drug exchange between amniotic sac and maternal circulation considered negligible.**
4. **The drug concentrations in fetal venous plasma equals to drug concentrations in umbilical cord plasma.**

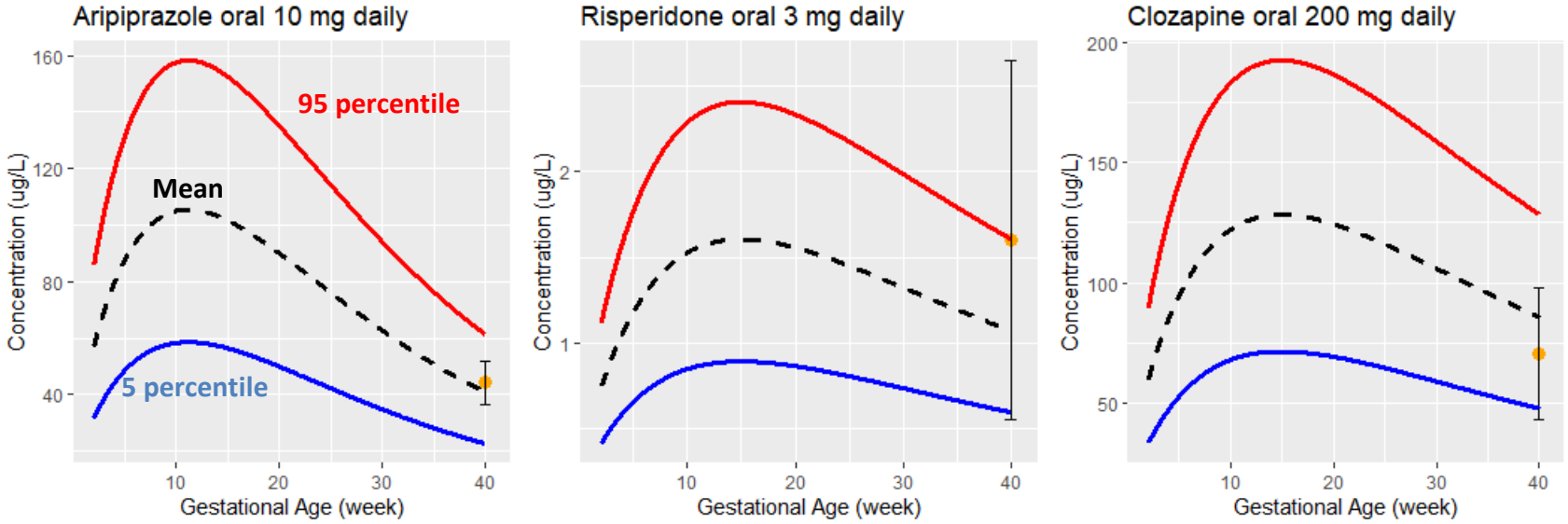


# Maternal-Fetal Model Simulation

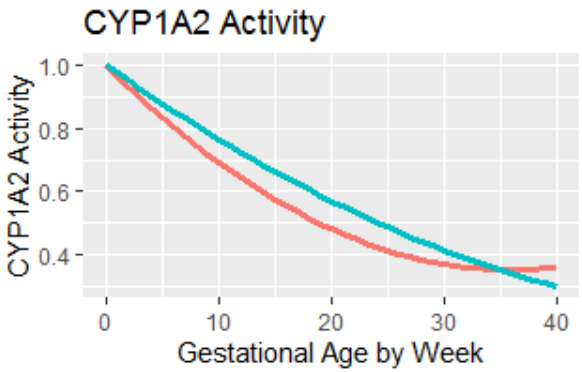
## Observed data from previous reports

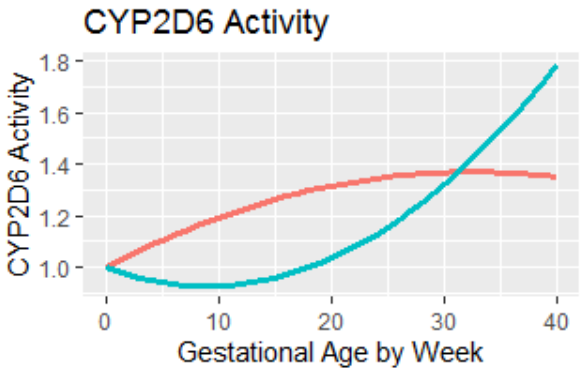
| | Drug Concentrations in Umbilical Cord Plasma | | | Dose (mg/day) | References |
|---|---|---|---|---|---|
| | n | Mean (ng/mL) | SD | | |
| **Aripiprazole** | 3 | 44.33 | 7.76 | 10 mg/day | Windhager et al. 2014 |
| **Risperidone** | 6 | 1.6 | 1.05 | 3 mg/day | Newport et al. 2007 |
| **Clozapine** | 5 | 70.4 | 27.4 | 200 mg/day | Imaz et al. 2018 |

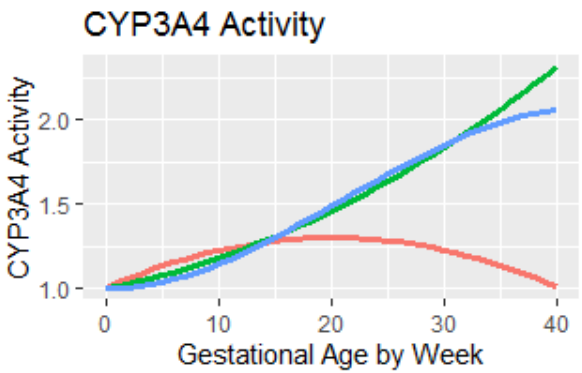
### Umbilical Cord Plasma Concentrations of Antipsychotics



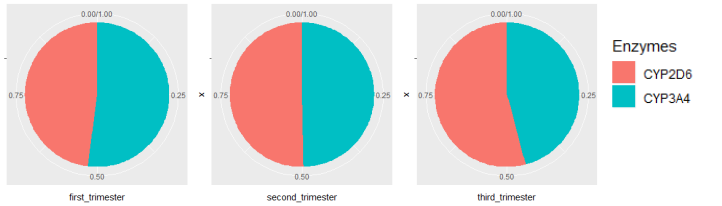
# Flexible to Keep up with Current Research

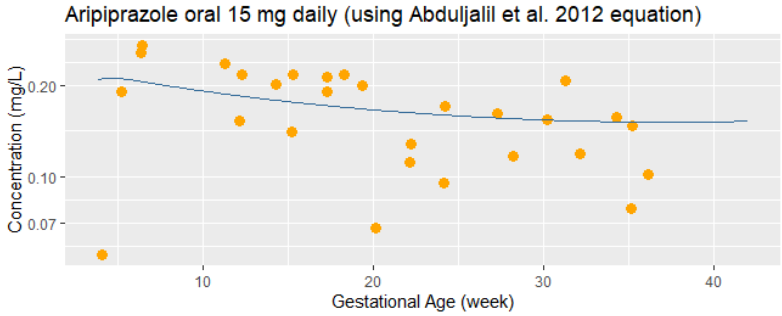


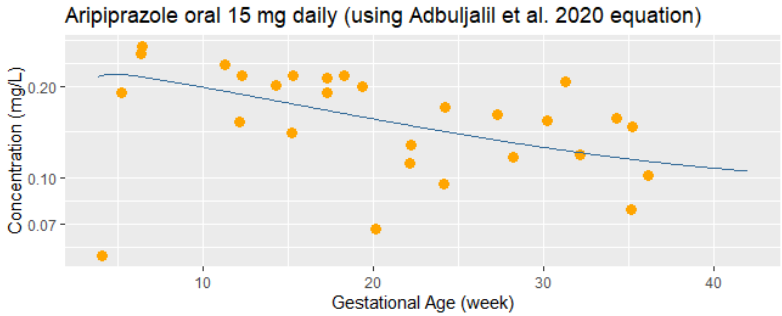



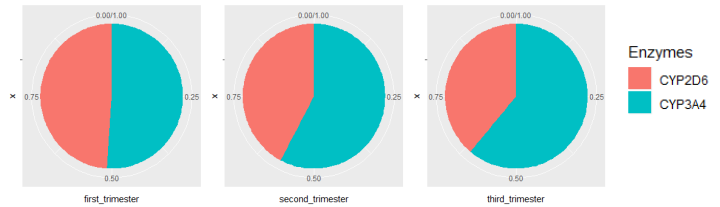










Abduljalil et al. 2012 (PMID: 22515555); Abduljalil et al. 2020 (PMID: 32840724); Ke et al. 2019 (PMID: 30924921)

# Conclusions

- Pregnancy and maternal-fetal PBPK is a useful tool to predict the intra-uterine exposure
- The population model based on the demographics of real population can help advance the variability assessment in these susceptible populations
- Maternal-fetal PBPK model can help determine the safety and efficacy of therapeutic agents and can also be adapted for chemical risk assessment as necessary

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