Predicting Drug Exposure in Fetus and Genital Tract During Pregnancy

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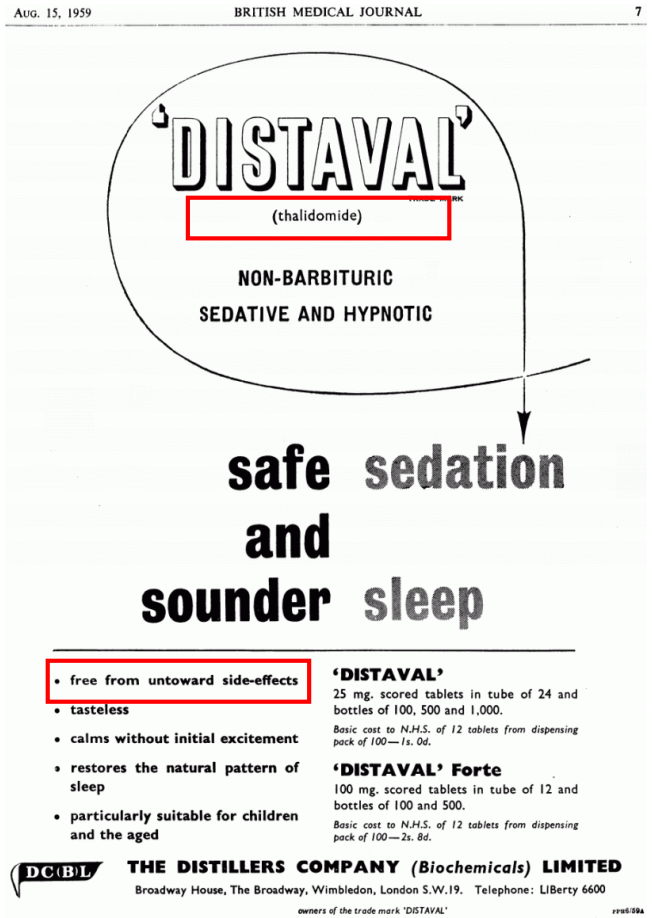
UNIVERSITY OF LIVERPOOL | CELT



Aug. 15, 1959 BRITISH MEDICAL JOURNAL 7

'DISTAVAL'

(thalidomide)

NON-BARBITURIC

SEDATIVE AND HYPNOTIC

safe sedation and sounder sleep

- free from untoward side-effects
- tasteless
- calms without initial excitement
- restores the natural pattern of sleep
- particularly suitable for children and the aged

'DISTAVAL'

25 mg. scored tablets in tube of 24 and bottles of 100, 500 and 1,000.

Basic cost to N.H.S. of 12 tablets from dispensing pack of 100—1s. 0d.

'DISTAVAL' Forte

100 mg. scored tablets in tube of 12 and bottles of 100 and 500.

Basic cost to N.H.S. of 12 tablets from dispensing pack of 100—2s. 8d.

DCBL **THE DISTILLERS COMPANY (Biochemicals) LIMITED**

Broadway House, The Broadway, Wimbledon, London S.W.19. Telephone: LIBerty 6600

owners of the trade mark 'DISTAVAL'

Tracey standing on block feet with articulated knees

Six pairs of prosthetic limbs made for Tracey Baynam who was exposed to thalidomide *in utero*.

Sources: https://www.sciencemuseum.org.uk/ and https://wellcomecollection.org/

Outline

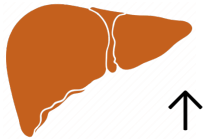
- Brief overview of modelling approach for key aspects:
  - Maternal adaptation to pregnancy (hepatic metabolism)
  - Foetal circulation
  - Gestational-age dependent changes in foetal organs
- Examples:
  - PBPK model of prenatal exposure to thalidomide vs efavirenz
  - Modelling drug distribution into female genital tract (FGT)
- Lessons and limitations

Maternal Adaptations to Pregnancy

↑GFR
↑Secretion CL
↑BUN, Creatinine, uric acid

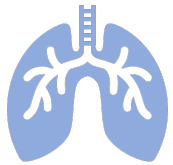
↑Uterus size & weight
↑ Fibrous connective tissues
Cervical softening
↑Vaginal size
Hyperplasia of lining
↑Estrogen influence

↑Blood volume
↑Heart rate
↑Size

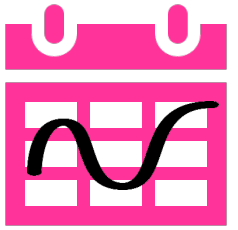


↑↓CYP P450 enzymes
↑Estradiol influence

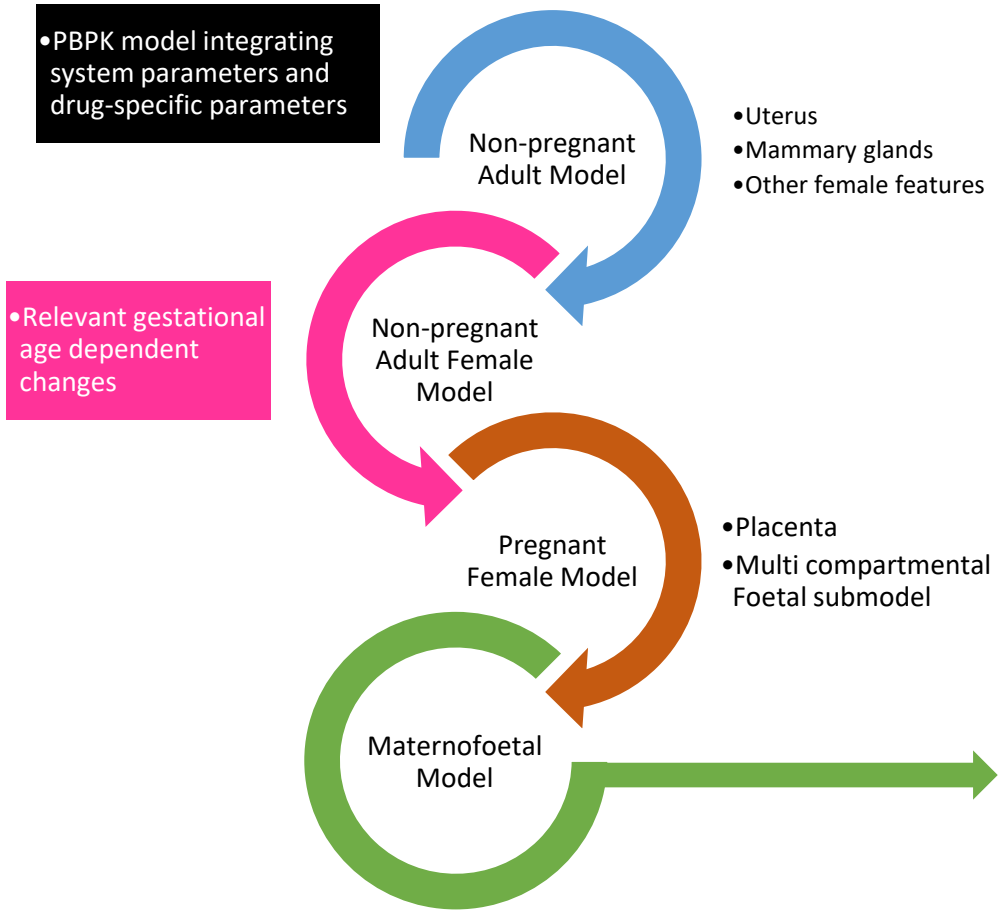
Produces HCB, HPL
Receives foetal waste
Transfers nutrients to foetal
Secretes hormones

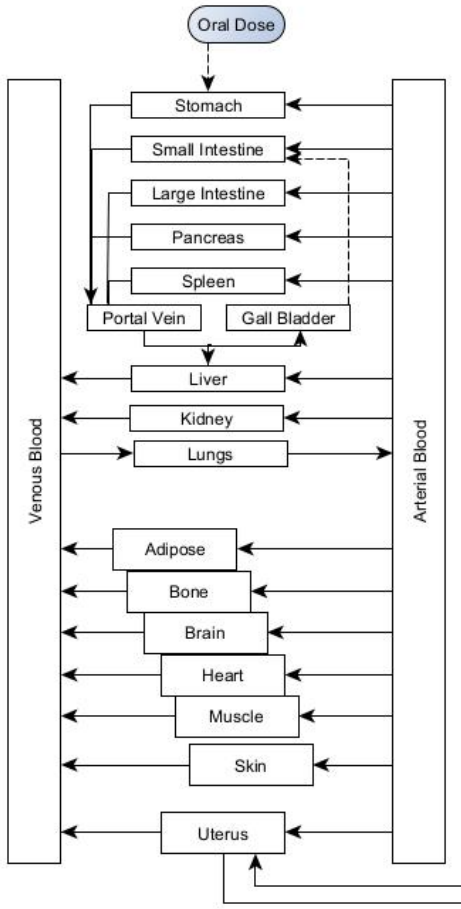


↑Tidal volume
↑Oxygen consumption

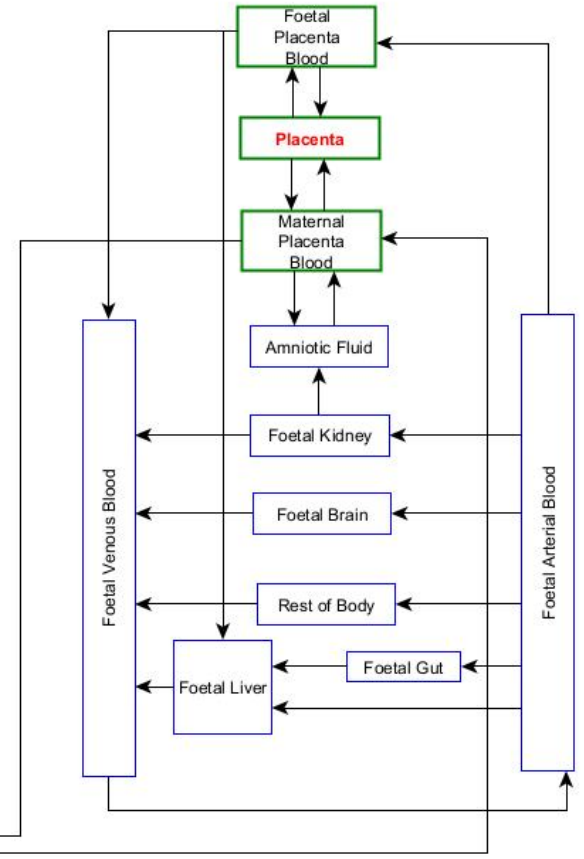


Prenatal Drug Exposure Model Workflow



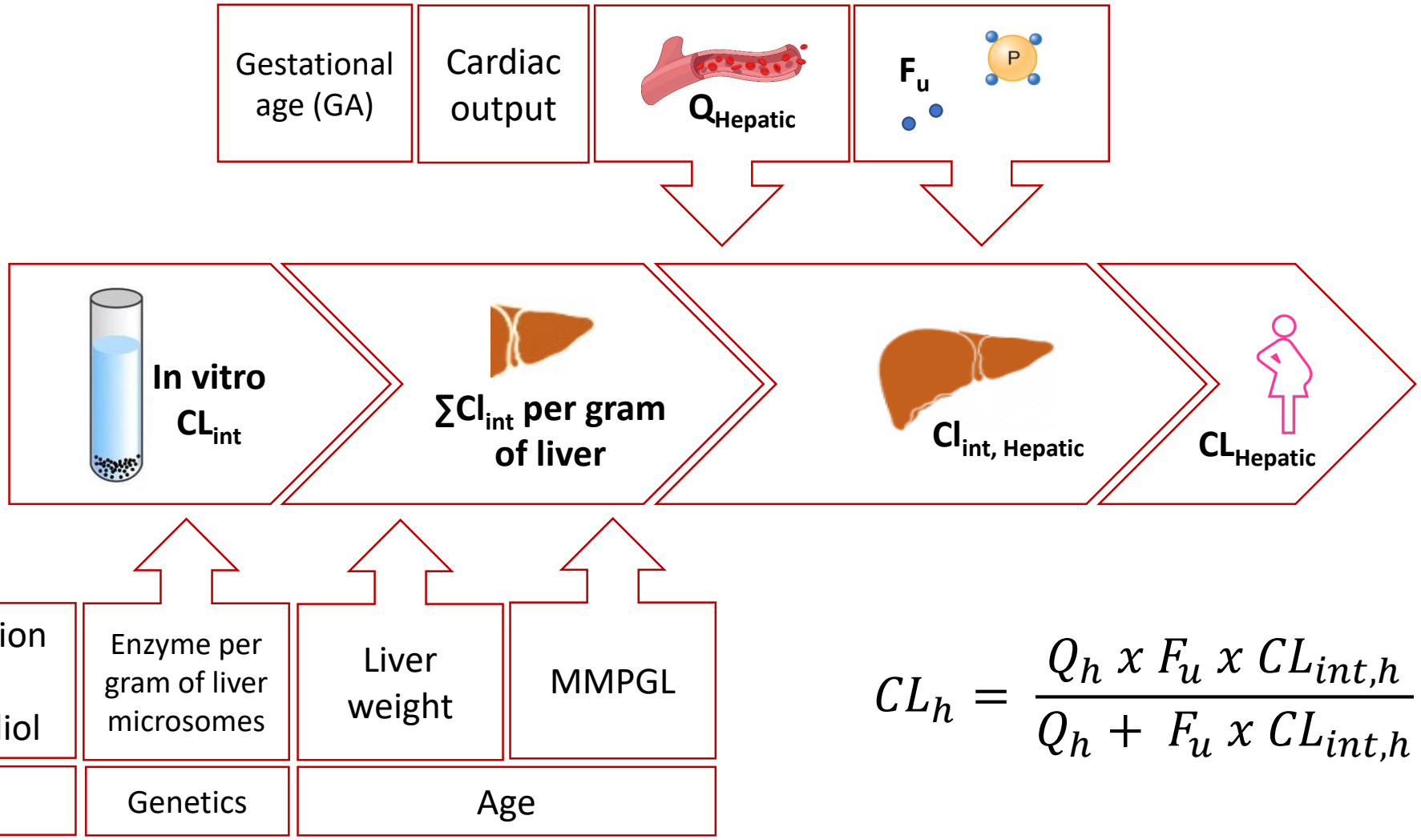


Olagunju et al. *AAS Open Res* **1**:16 (2018)



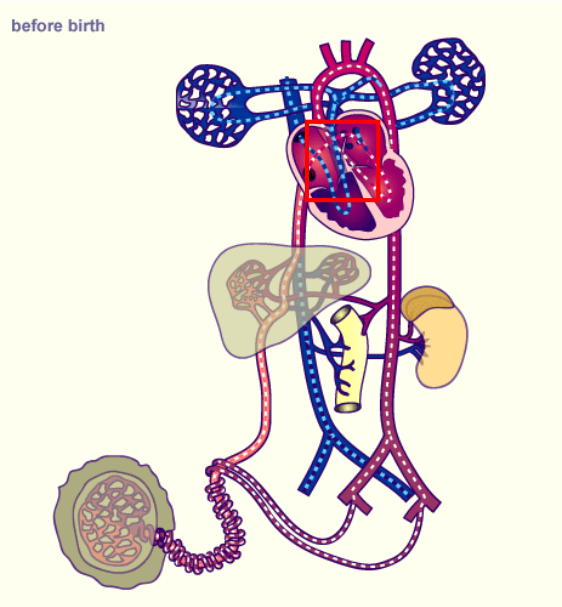
Zhang et al. *Drug Metab Dispos* 45, 920-938 (2017)

Modelling Maternal Hepatic Metabolism

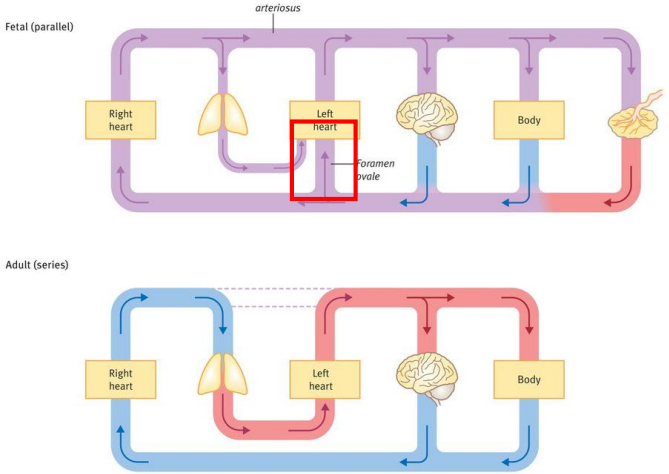


$$CL_h = \frac{Q_h \; x \; F_u \; x \; CL_{int,h}}{Q_h + \; F_u \; x \; CL_{int,h}}$$

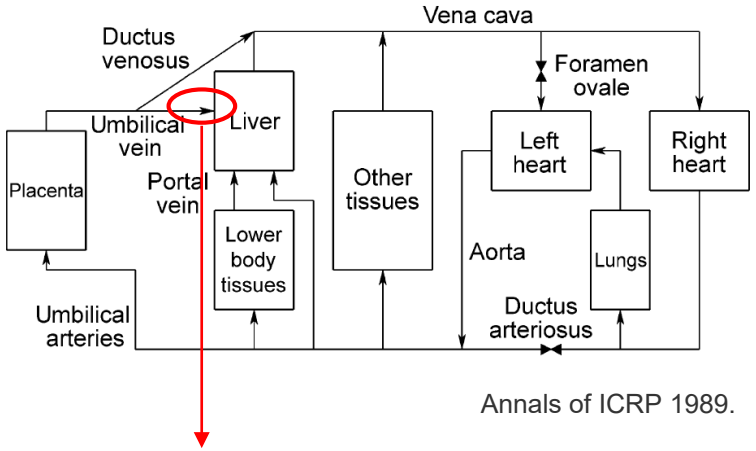
Modelling Foetal Circulation



Source: https://www.embryology.ch/



Source: https://obgynkey.com/fetal-physiology-3/



Annals of ICRP 1989.

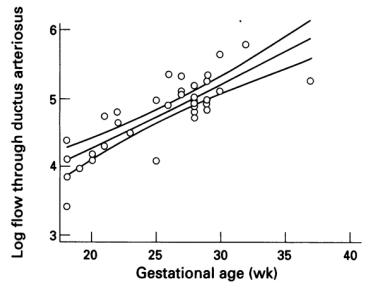


Figure 4 Relation between logarithm (ln) of flow in the ductus arteriosus and gestational age with 95% CIs.

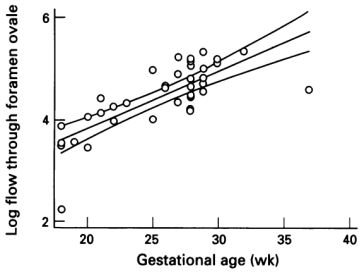


Figure 6 Relation between logarithm (ln) of flow through the foramen ovale and gestational age with 95% CIs.

Sutton et al. *Heart* 1994;**71:**232-237

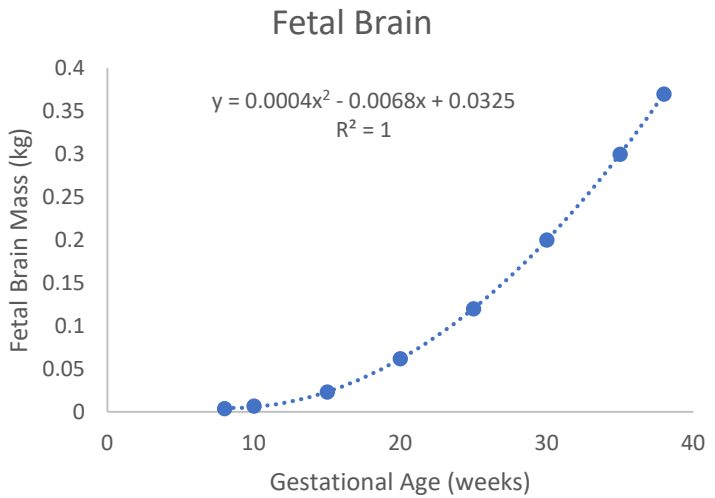
$$\frac{dD_i}{dt}_i = \frac{1}{V_i} \cdot \left((Q_i \,.\, D_i) - \left(Q_i \frac{D_i}{P_i} \right) \right)$$

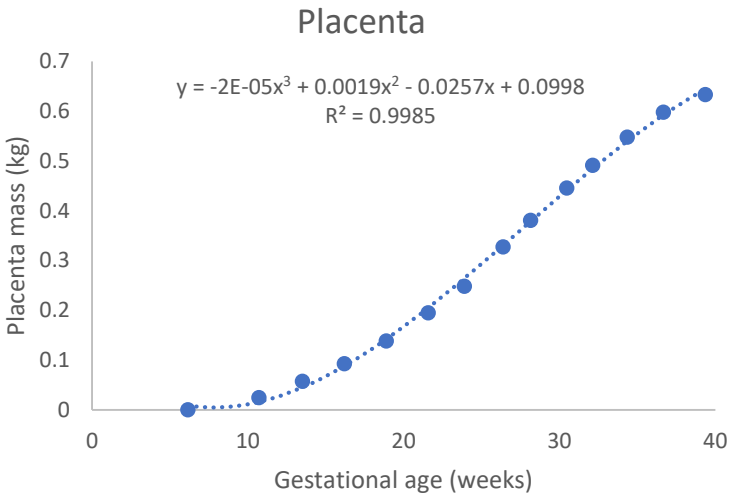
$$Q_{umv} = 0.647 - 0.227 * XGA + 0.0179 * XGA^2$$

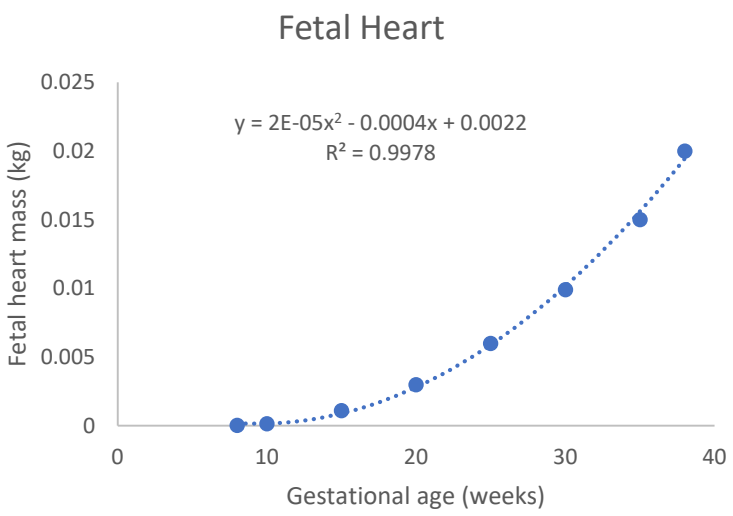
$$Q_{dv} = 2.05 - 0.297 * XGA + 0.0116 * XGA^2$$

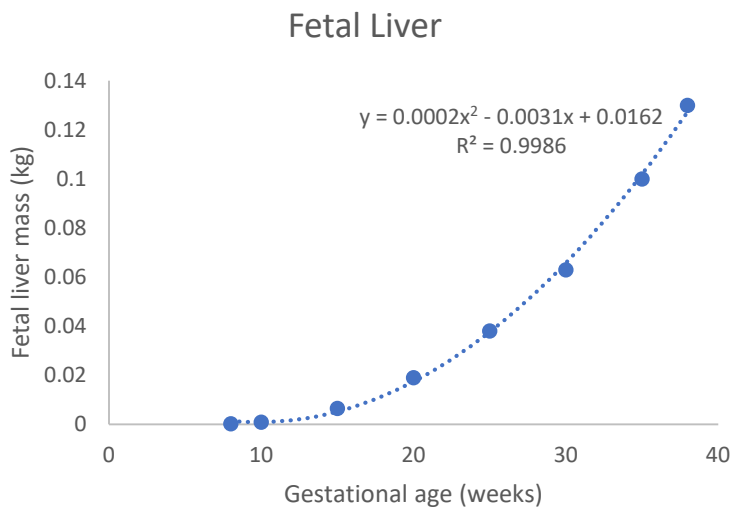
$$Q_{ps} = Q_{umv} - Q_{dv}$$

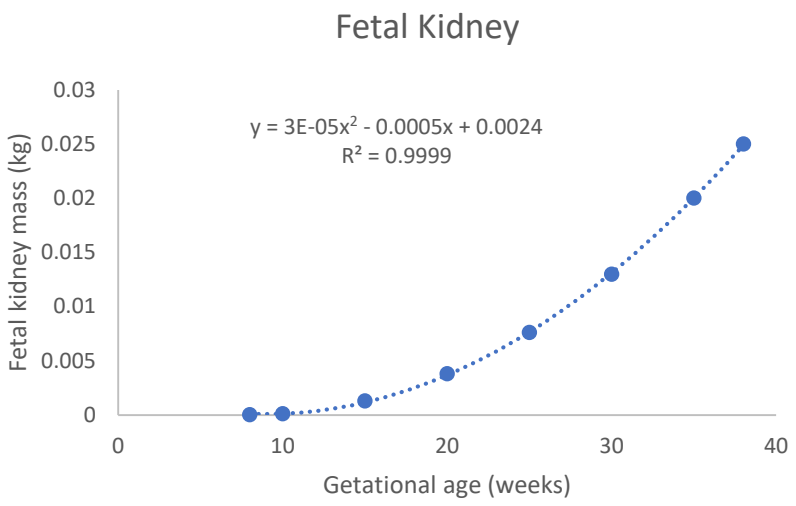
Modelling Foetal Organs



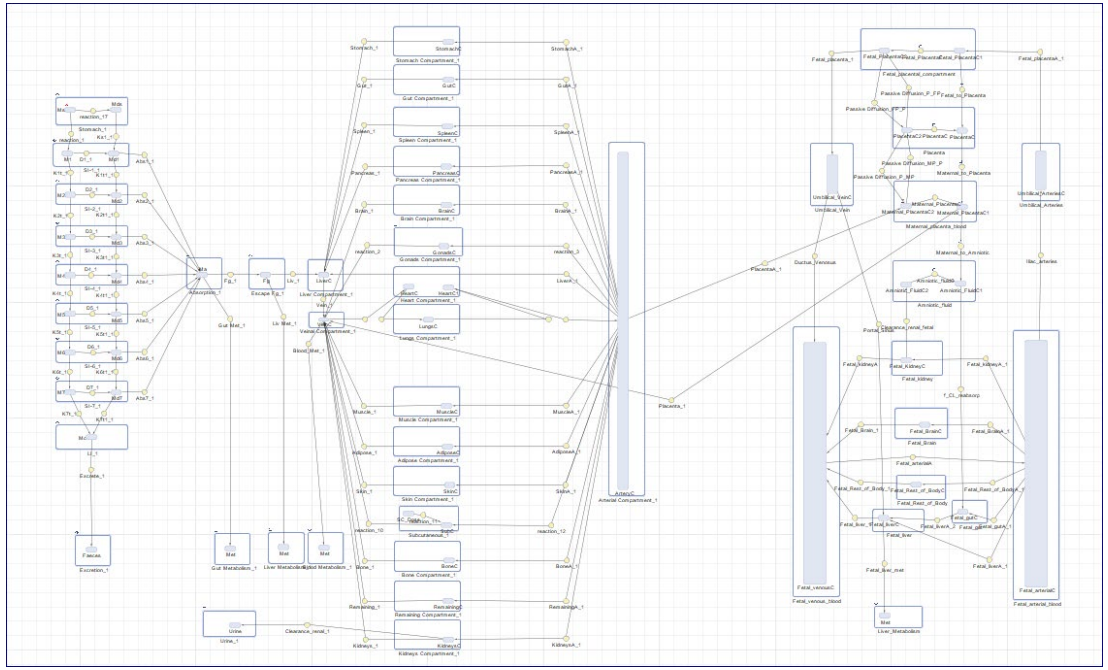








Final Model Structure



	Name
1	Variability = 0
2	Test Subject: Rat
3	Test Subject: Human
4	Route: Oral (Adult)
5	Drug: Efavirenz_mother
6	Drug: Thalidomide_mother
7	Drug: Efavirenz_backup
8	Drug: Dolutegravir_mother
9	Drug: Rilpivirine_mother

Component Name	Value
fu_1	0.015
pKa_1	10.2
Kpc_1	4.6
R_1	0.74
Clint2A6_1	0.05
Clint2B6_1	0.55
Clint3A4_1	0.007
Clint1A2_1	0.008
Clint3A5_1	0.03
Caco_1	2.5E-6

Species | Parameters | Rules | Reactions | Variants | Doses

Enter Rule: Add Delete

	Name	Rule	RuleType	Active
40	Enzyme expression - Abundance - CYP3A5_1	Abundance_CYP3A5_1 = abs(normrnd(16,5))	initialAssignment	☑
41	Enzyme expression - Abundance - CYP3A7_fetal	Abundance_CYP3A7_f = abs(normrnd(200.9,111.3))	initialAssignment	☑
42	Enzyme expression - Activity - CYP1A2_Pregnant (%)	Activity_CYP1A2 = 100-3.5814*XGA+0.0495*XGA^2	initialAssignment	☑
43	Enzyme expression - Activity - CYP2D6_Pregnant (%)	Activity_CYP2D6 = 100+2.2695*XGA-0.0348*XGA^2	initialAssignment	☑
44	Enzyme expression - Activity - CYP3A4_Pregnant (%)	Activity_CYP3A4 = 100+2.9826*XGA-0.0741*XGA^2	initialAssignment	☑
45	AUC - plasma conc	AUCplasma = Plasma_conc_1	rate	☑
46	AUC - plasma conc_1	AUCvc_1 = Plasma_conc_1	rate	☑

Settings | Description

Name:

Enzyme expression - Activity - CYP3A4_Pregnant (%) ☑ Active

Rule:

Activity_CYP3A4 = 100+2.9826*XGA-0.0741*XGA^2

1. Prenatal Drug Exposure: Thalidomide vs Efavirenz

ELSEVIER

European Journal of Pharmaceutical Sciences
Volume 140, 1 December 2019, 105068

Using mechanistic physiologically-based pharmacokinetic models to assess prenatal drug exposure: Thalidomide *versus* efavirenz as case studies

Shakir Adeyinka Atoyebi [a], Rajith K.R. Rajoli [b], Ebunoluwa Adejuyigbe [c], Andrew Owen [b], Oluseye Bolaji [a], Marco Siccardi [b], Adeniyi Olagunju [a, b]

- Characterise prenatal drug exposure across gestation.
- Model organ-level prenatal drug exposure.
- Compare thalidomide vs efavirenz using qualified models.

Model Qualification for Non-pregnant Adults

Parameters	Observed	Predicted	Predicted/observed ratio
Efavirenz[a]	(Dickinson et al., 2016) n = 605	n = 100	
400 mg			
C_{12} (mg/L)	2.10 (2.01–2.20)	1.86 (1.65–2.06)	0.89
C_{24} (mg/L)	1.40 (1.32–1.49)	1.30 (1.10–1.49)	0.93
C_{max} (mg/L)	2.52 (2.42–2.62)	2.47 (2.27–2.67)	0.98
AUC_{0-24} (mg.h/L)	49.2 (47.0–51.5)	42.6 (38.0–47.2)	0.87
600 mg			
C_{12} (mg/L)	2.85 (2.70–3.0)	2.93 (2.59–3.27)	1.0
C_{24} (mg/L)	1.82 (1.68–1.97)	2.07 (1.75–2.40)	1.1
C_{max} (mg/L)	3.66 (3.51–3.81)	3.86 (3.52–4.20)	1.1
AUC_{0-24} (mg.h/L)	67.2 (63.8–70.9)	67.3 (59.5–75.0)	1.0
Thalidomide[b]	Thalomid Label_FDA (2001)	n = 100	
200 mg			
C_{max} (mg/L)	1.76 (30)	2.15 (17.7)	1.2
AUC_{0-24} (mg.h/L)	18.9 (17)	16.1 (18.6)	0.85
400 mg			
C_{max} (mg/L)	2.82 (28)	4.33 (18.2)	1.5
AUC_{0-24} (mg.h/L)	36.4 (26)	32.4 (18.5)	0.89

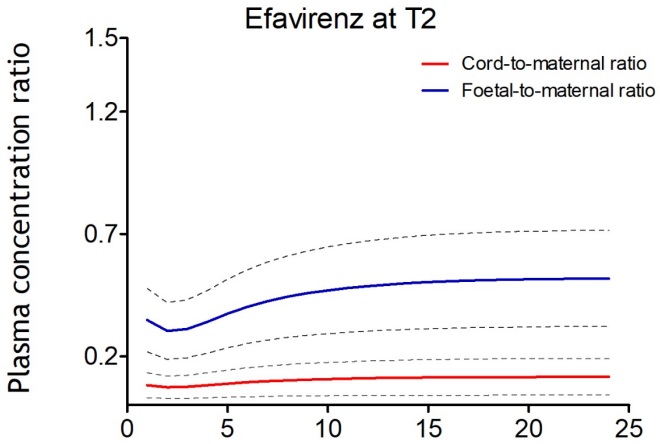
[a] Mean (90% CI) at steady-state.
[b] Mean (%CV) after single dose.

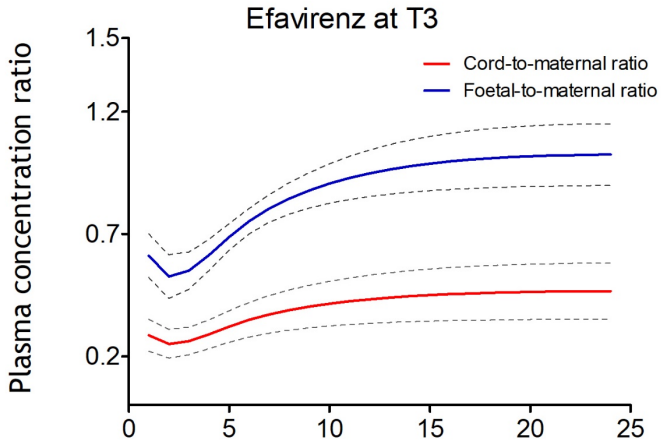
Model Qualification for Pregnant Women

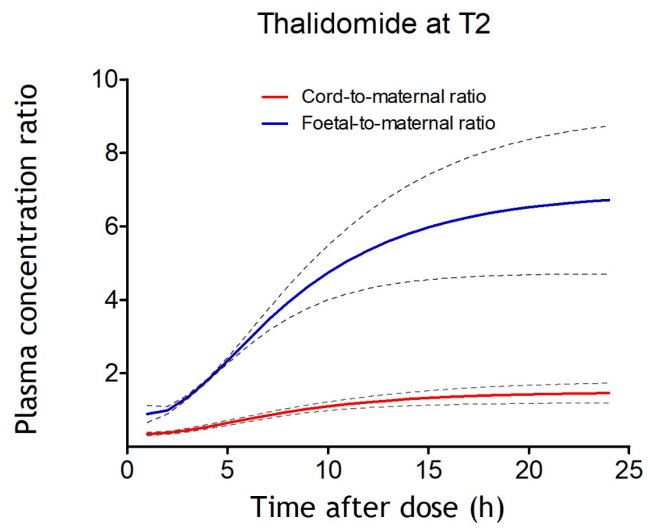
Pharmacokinetic parameter (units)	Observed values	Simulated values	Predicted/observed ratio
400 mg efavirenz[a]			
Third trimester	(Lamorde et al., 2018) n = 25	n = 100	
C_{min} (mg/L)	1.21 (0.878–1.65)	1.07 (0.915–1.23)	0.88
C_{max} (mg/L)	2.75 (2.25–3.36)	2.11 (1.94–2.28)	0.77
AUC_{0-24} (mg.h/L)	39.9 (30.8–51.7)	35.6 (31.7–39.4)	0.89
600 mg efavirenz[b]			
Throughout pregnancy	(Olagunju et al., 2015a) n = 25	n = 100	
C_{min} (mg/L)	1.00 (0.429–5.19)	1.44 (0.303–8.61)	1.4
C_{max} (mg/L)	3.49 (1.26–14.4)	2.97 (1.50–9.82)	0.85
CL/F (L/h)	14.1 (2.96–27.7)	12.1 (2.84–32.5)	0.86
AUC_{0-24} (mg.h/L)	42.6 (21.7–203)	49.5 (18.4–211)	1.2
Third trimester	(Cressey et al., 2012) n = 25	n = 100	
C_{min} (mg/L)	1.60 (0.23–8.13)	1.20 (0.237–12.1)	0.75
C_{max} (mg/L)	5.44 (1.90–12.2)	2.72 (1.46–13.4)	0.50
CL/F (L/h)	10.8 (2.7–44.4)	13.8 (2.05–36.0)	1.3
AUC_{0-24} (mg.h/L)	55.4 (13.5–220)	43.5 (16.9–292)	0.79
At delivery			
Umbilical vein	(Cressey et al., 2012) n = 23	n = 100	
Efavirenz concentration (mg/L)	1.05 (0.47–4.51)	0.745 (0.341–3.84)	0.71
C:M ratio	0.49 (0.37–0.74)	0.47 (0.42–0.58)	0.97
Foetal plasma	(Gandhi et al., 2013) n = 50	n = 100	
Efavirenz concentration (mg/L)	1.70 (0.050–7.88)	1.47 (0.654–7.92)	0.86

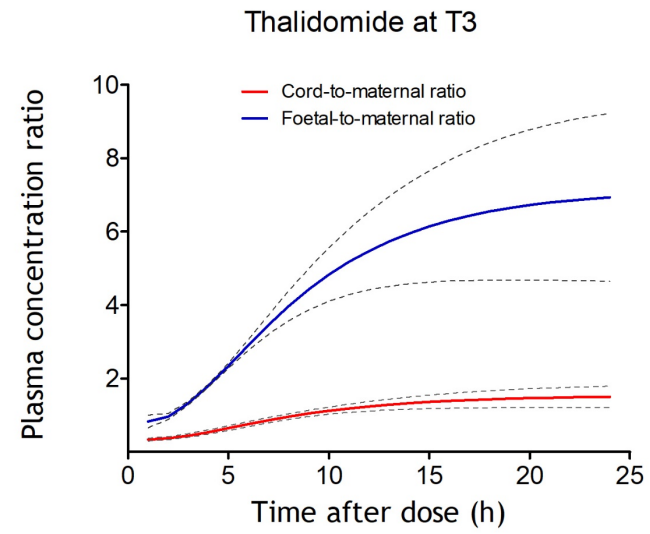
[a] Data presented as mean (95% Confidence Interval).
[b] Data presented as median (range).

Foetal Exposure Indices: Thalidomide vs Efavirenz







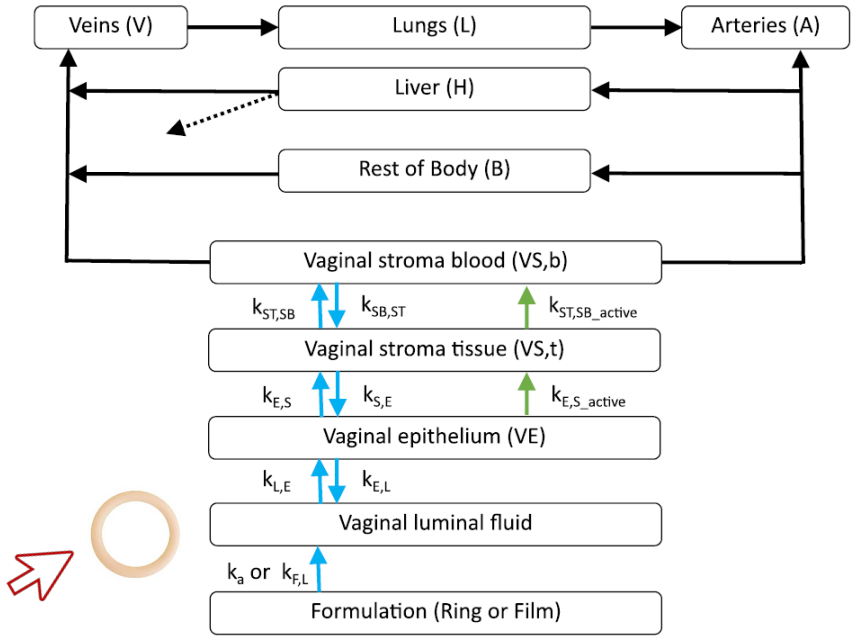


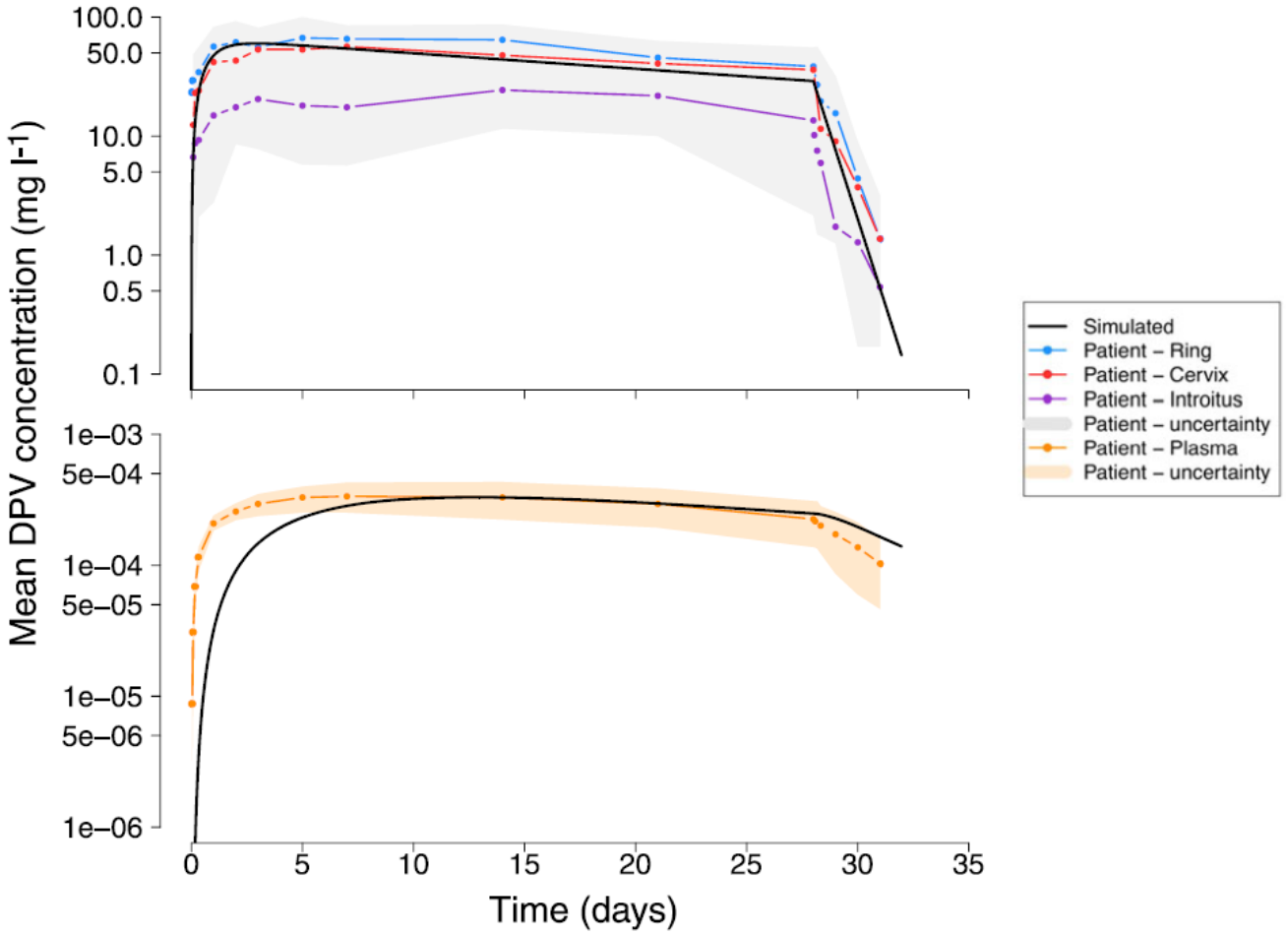
Efavirenz brain PK	T2	T3
FB conc. (mg/L)	0.073	0.11
$AUC_{0\text{-}24}$ (mg.h/L)	1.69	2.49
AUC $ratio_{FB:MP}$	0.05	0.09

Thalidomide brain PK	T2	T3
FB conc. (mg/L)	4.28	4.31
$AUC_{0\text{-}24}$ (mg.h/L)	101	102
AUC $ratio_{FB:MP}$	4.61	4.56

**FB, foetal brain; MP, maternal plasma*

2. Modelling Drug Distribution in Female Genital Tract





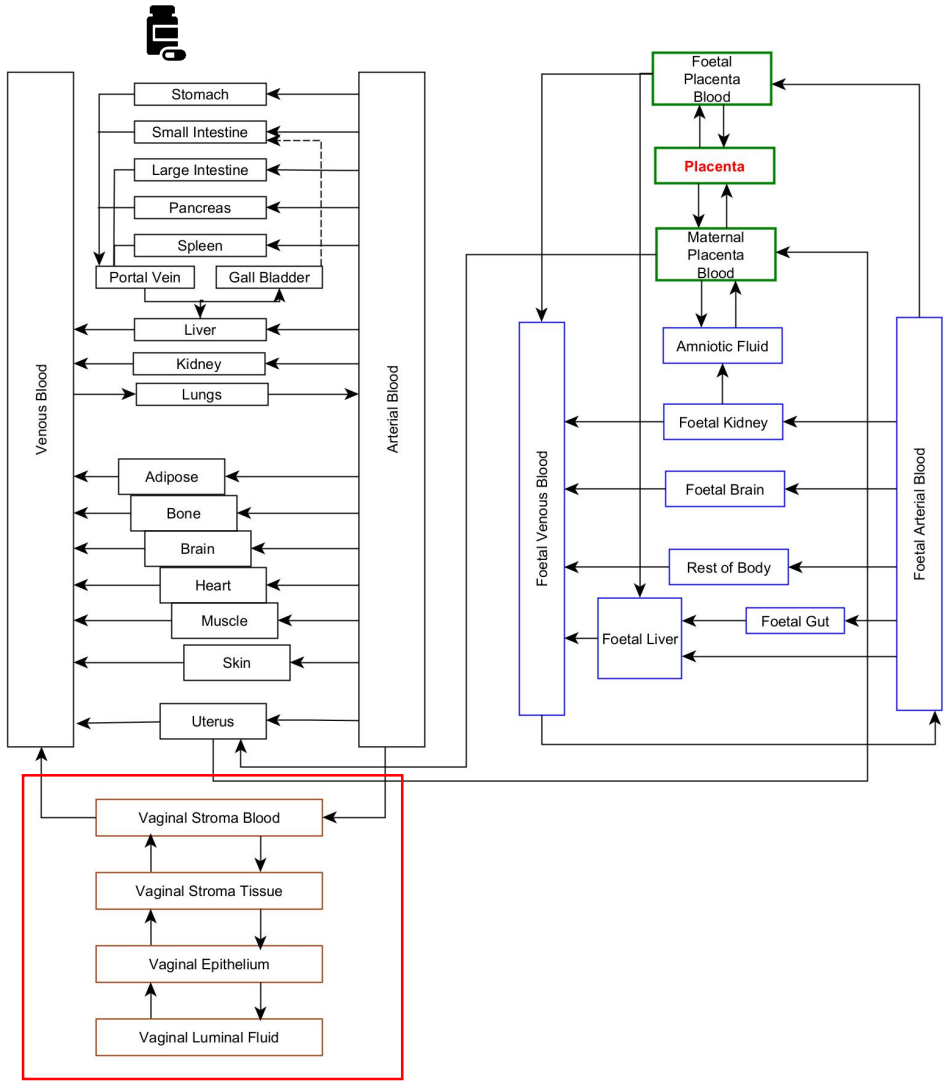
$$\frac{dD_{Lumen}}{dt} = \frac{1}{V_{lumen}} \cdot [\mathrm{DR_{Formulation}} - ((\mathrm{k_{L,E}} \cdot \mathrm{D_{Lumen}}) \cdot V_{\mathrm{Lumen}} - (k_{E,L} \cdot D_{VE}) \cdot V_{VE}) - ((\mathrm{I_{Lumen}} \cdot \mathrm{D_{Lumen}}) \cdot V_{\mathrm{Lumen}} - (\mathrm{UI} \cdot D_{IonLumen}) \cdot V_{Lumen})]$$

$$\frac{dD_{\mathrm{Ring}}}{dt} = -\left(\left(\mathrm{k_a} \cdot e^{(k_{a\_\exp} \cdot (t - t_{Ring}))}\right) \cdot \mathrm{D_{Ring}}\right)$$

$$\frac{dD_{\mathrm{Film}}}{dt} = \frac{1}{V_{Film}} \cdot -((\mathrm{k_{F,L}} \cdot \mathrm{D_{Film}}) \cdot V_{\mathrm{Film}})$$

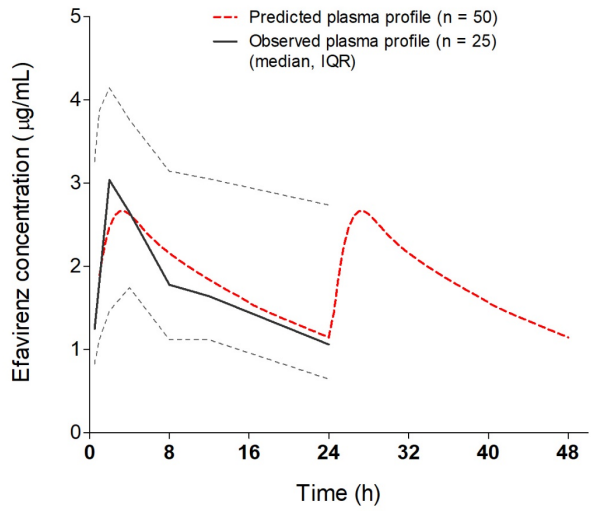
Kay et al. Br J Clin Pharmacol (2018) 84 1950–1969

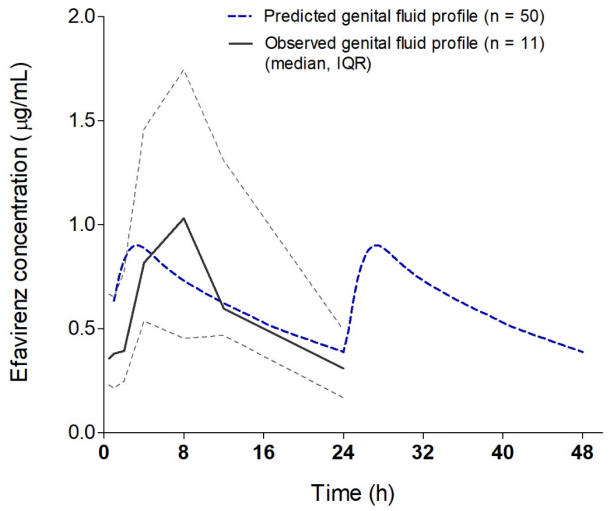
PBPK Model of Drug Distribution in FGT

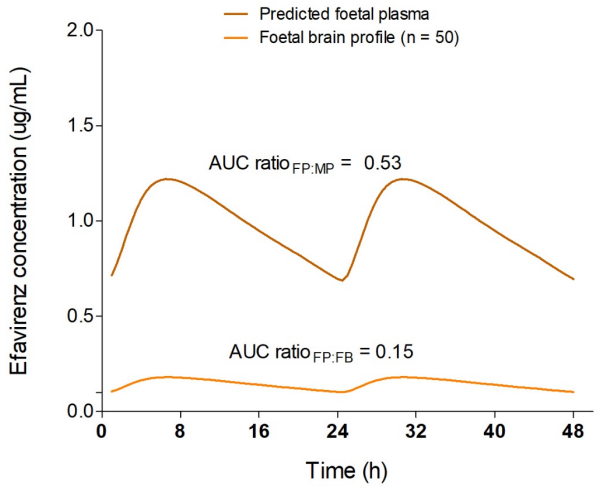


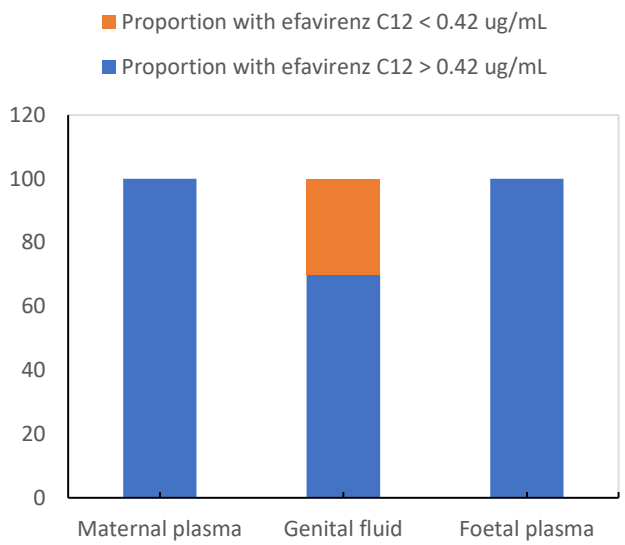
- Allows simultaneous assessment of foetal exposure and genital tract distribution.
- Several potential applications:
  - Determine optimal product characteristics for PrEP & PMTCT (e.g. intrapartum HIV) drug candidates.
  - Characterise foetal exposure to drugs administered intravaginally.
  - Drug release kinetics of modified release formulations added to extend application.

Efavirenz PK in Cervicovaginal Fluid









	Clinical	Predicted
Age (y)	29.5 (5.2)	30.7 (8.3)
GA (weeks)	28.4 (4.4)	33.5 (2.2)
Weight (kg)	66.3 (7.7)	72.4 (1.13)
Daily dose	600 mg	600 mg
Maternal plasma (MP)		
$AUC_{0\text{-}24}$ (µg.h/ml)	42.6	42.6
C_{min} (µg/ml)	1.00	1.14
C_{max} (µg/ml)	3.49	2.66
Cervicovaginal fluid (CVF)		
$AUC_{0\text{-}24}$ (µg.h/ml)	13.2	14.4
C_{min} (µg/ml)	0.242	0.388
C_{max} (µg/ml)	0.993	0.900
AUC ratio$_{CVF:MP}$	0.31	0.34

Lessons & Limitations

"Since all models are wrong the scientist must be alert to what is importantly wrong. It is inappropriate to be concerned about mice when there are tigers abroad." - Box, GEP. J Am Stat Assoc 71, 791–799 (1976).

- Modelling in this area is sometimes like looking for a needle in a haystack.
- Keys to progress include:
  - Access to robust clinical PK datasets from well conducted studies (e.g. validated bioanalytical method).
  - Know exactly what you're looking for (e.g. efficacy vs safety).
  - Collaborate to get other involved (e.g. share model equations libraries).
  - Understand what is "importantly wrong" per use case.
- Exposure metrics ≠ safety metrics.
- Employing new tools to bridge this gap will help to generate data that will inform decisions about early inclusion of pregnant women in clinical trials.

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