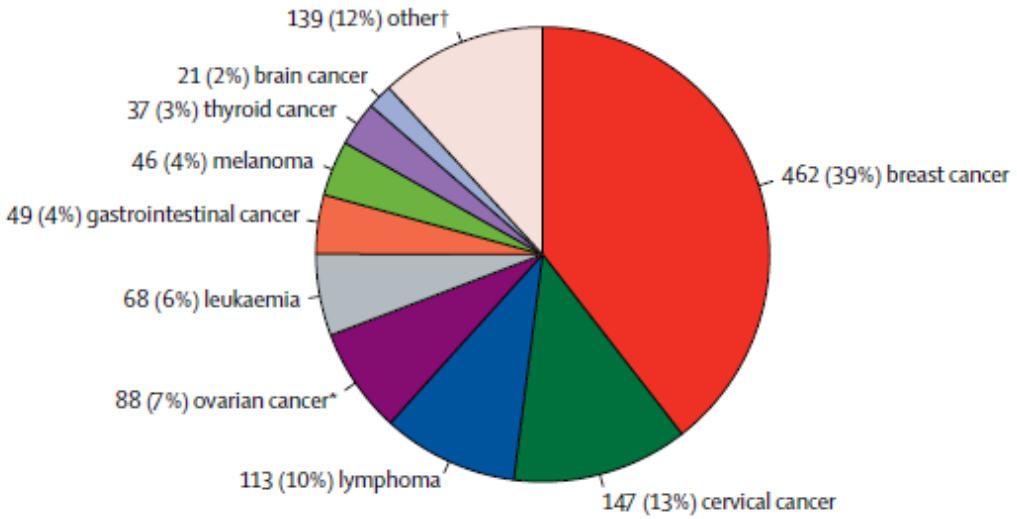
A semi-physiological framework to predict changes in pharmacokinetics of cytotoxic drugs in pregnant women

J.M. Janssen*, J.G.C. van Hasselt, K. van Calsteren, F. Amant, J.H. Beijnen, A.D.R. Huitema, T.P.C. Dorlo

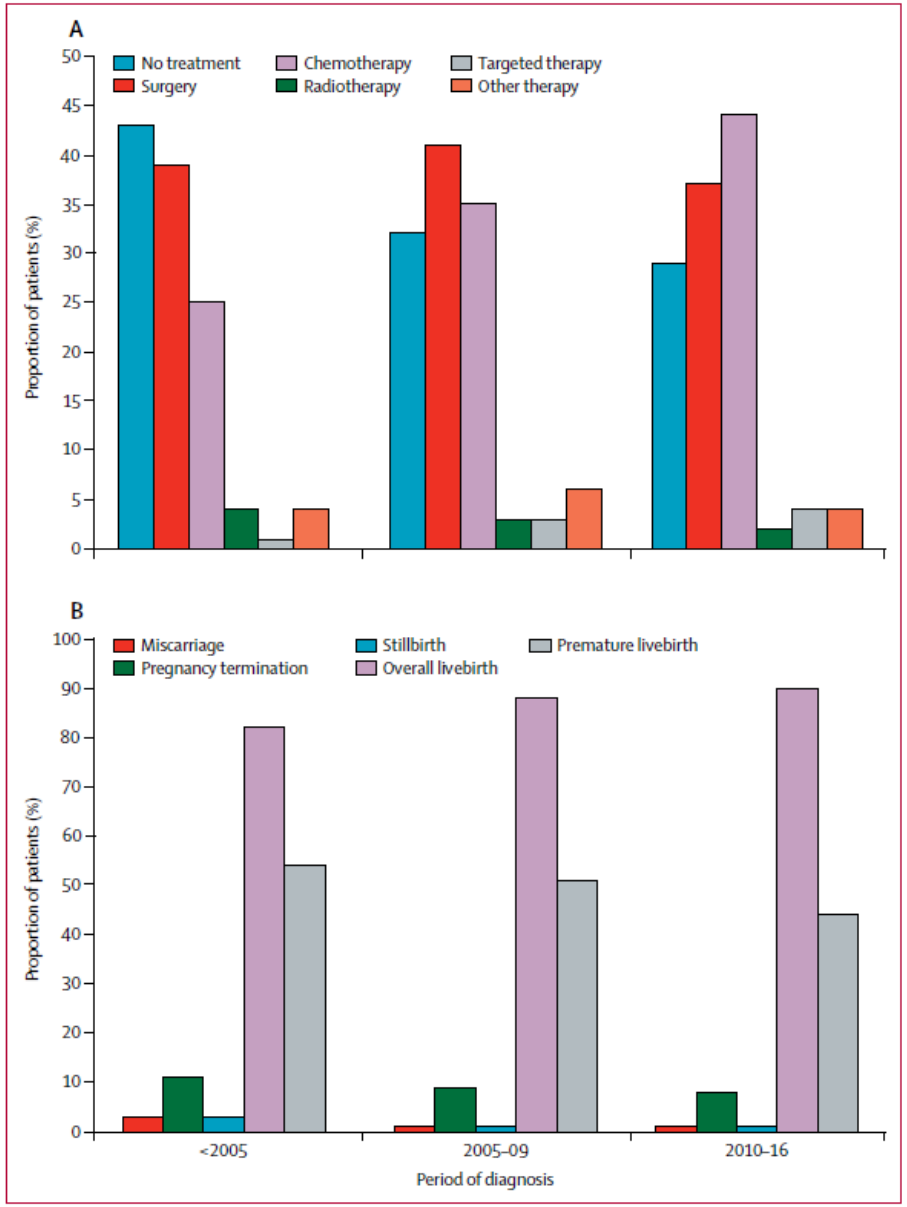
* PharmD, PhD candidate
Department of Pharmacy & Pharmacology, Antoni van Leeuwenhoek/Netherlands Cancer Institute, Amsterdam, The Netherlands

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Cancer occurs in one out of 1000 pregnancies



- 88% of singleton pregnancies ended in livebirth
- 37% treated with cytotoxic drugs
- Five (<1%) patients died during pregnancy



Physiological changes during pregnancy

CYP1A2 ↓
CYP2C19 ↓

CYP2D6 ↑
CYP3A4 ↑
CYP2C9 ↑
CYP2A6 ↑
CYP2E1 ↑
UGT1A4 ↑

Plasma protein concentrations ↓

Plasma volume ↑

GFR ↑
CRCL ↑

Intracellular water ↑

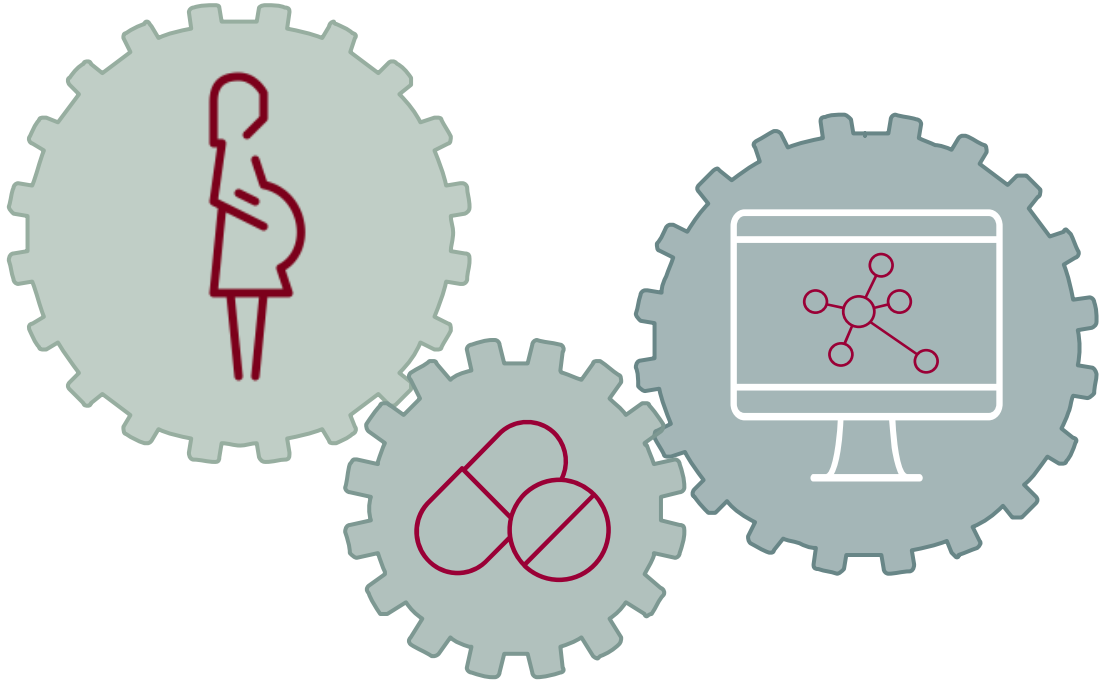
Total body water ↑

Why use a semi-physiological approach?

Aim

To combine existing knowledge of PK in non-pregnant patients with physiologically based PK modeling, to predict the PK of a range of cytotoxic drugs in pregnant patients

Approach



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Protein concentrations change over pregnancy

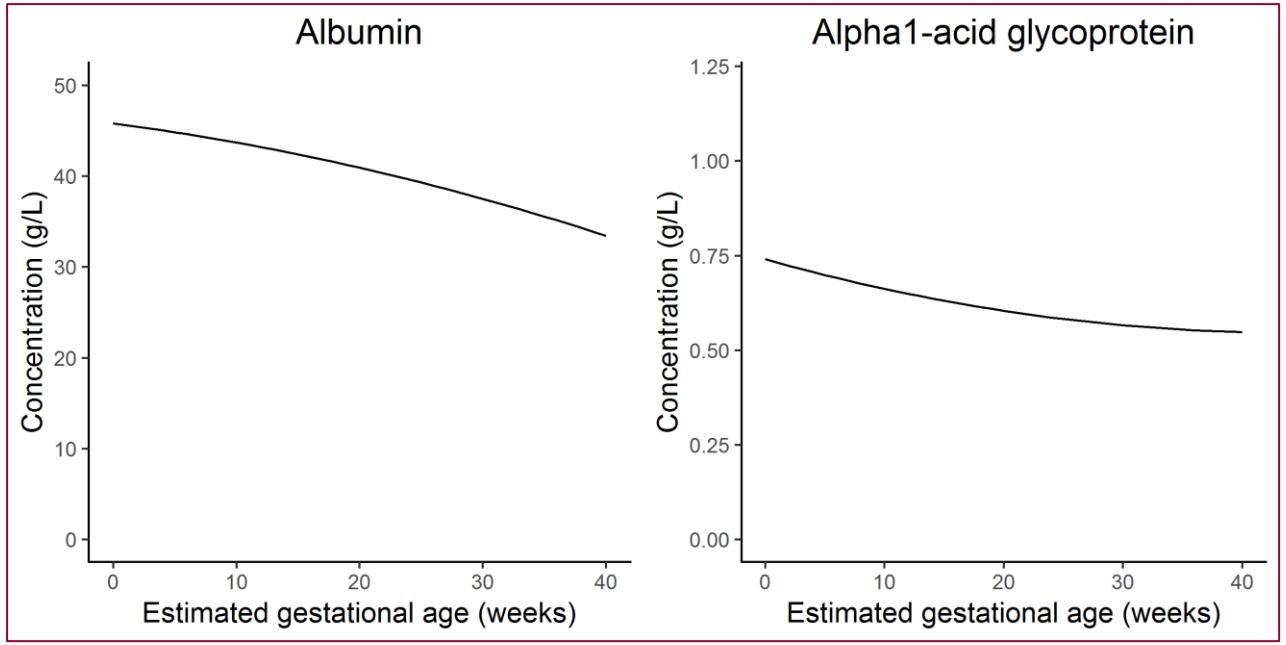
$$f_u = \frac{(K_D + [P])}{(B_{max} + K_D + [P])} \longrightarrow f_u = \frac{K_D}{(K_D + [P])}$$

Unknown K_D

$$K_D = -\frac{[P] \times f_u}{(f_u - 1)}$$

$$[\mathrm{P}]_{\mathrm{albumin}}\ (t)\ [\mathrm{g/L}] = 45.8 + 0.1775t - 0.0033t^2$$

$$[\mathrm{P}]_{\mathrm{agp}}\ (t)\ [\mathrm{g/L}] = 0.74 + 0.0088t - 0.0001t^2$$



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Simulation framework:
Clearance (hepatic)

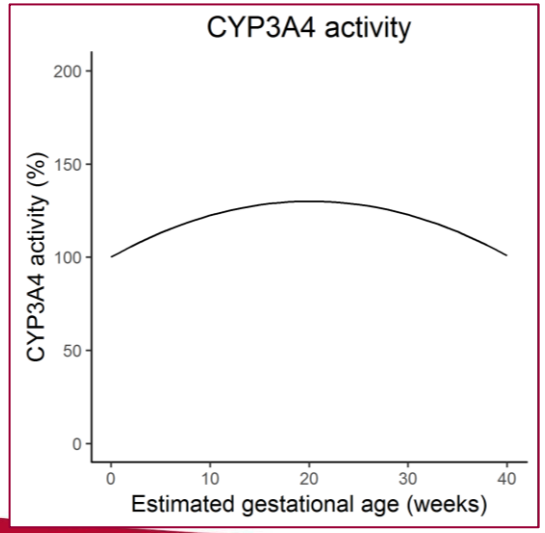
$$CL_R = CL \times fr \longleftarrow CL = CL_R + CL_H \longrightarrow CL_H = CL \times (1 - fr)$$

$$CL_H = \frac{Q_H \times CL_{int}}{Q_H + CL_{int}}$$

Unknown

$$CL_{int} = -\left(\frac{CL_H \times Q_H}{CL_H - Q_H}\right) \longrightarrow CL_{int}(t) = CL_{int} \times \left(\frac{E(t)}{100}\right)$$

$$CYP3A4\ (t)[\%] = 100 + 2.9826t - 0.0741t^2$$



NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

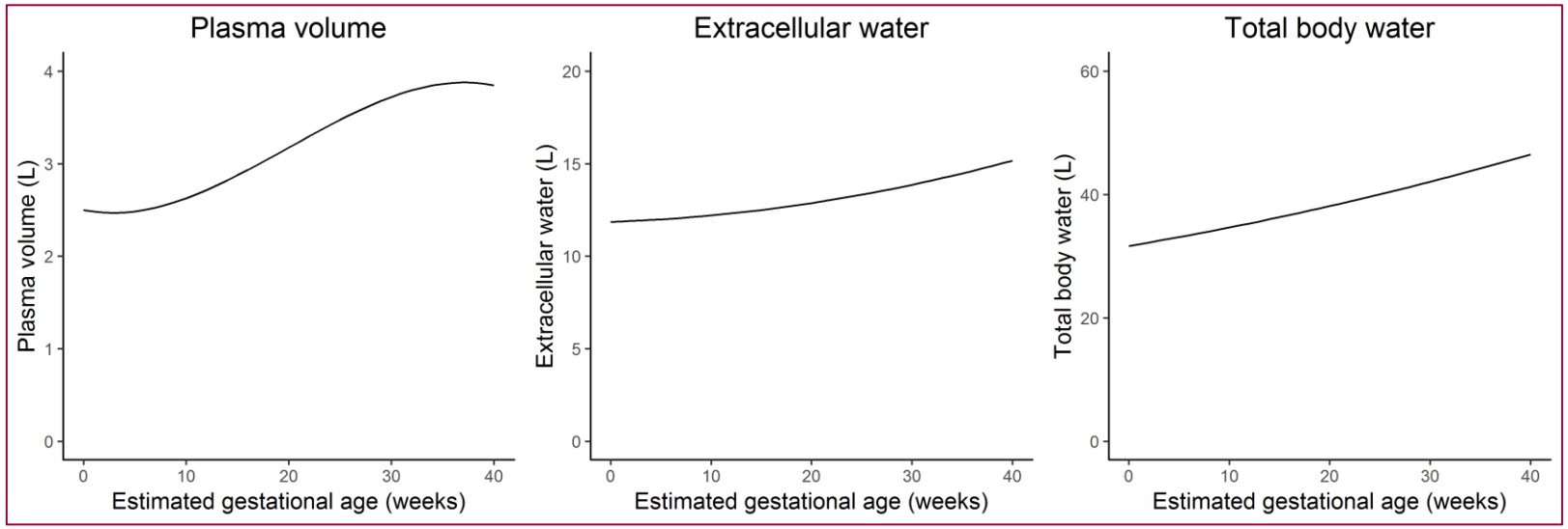
Simulation framework:
Volumes of distribution

$$V_d[L] = V_{plasma} + [V - V_{plasma}]\frac{f_u}{f_t}$$

Unknown

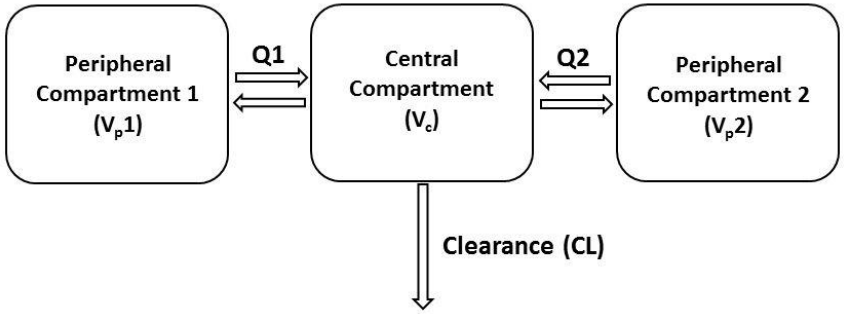
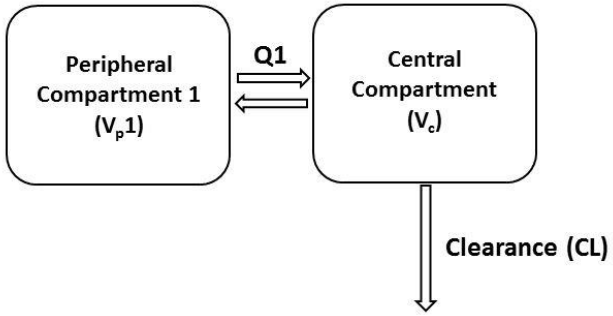
$$\frac{f_u}{f_t} = \frac{V_d - V_{plasma}}{[V - V_{plasma}]}$$

$$ECW(t)\,[L] = 11.86 + 0.0187t + 0.0016t^2$$
$$TBW(t)\,[L] = 31.67 + 0.275t + 0.0024t^2$$
$$V_{plasma}(t)\,[L] = 2.5 - 0.0223t + 0.0042t^2 - 0.00007t^3$$



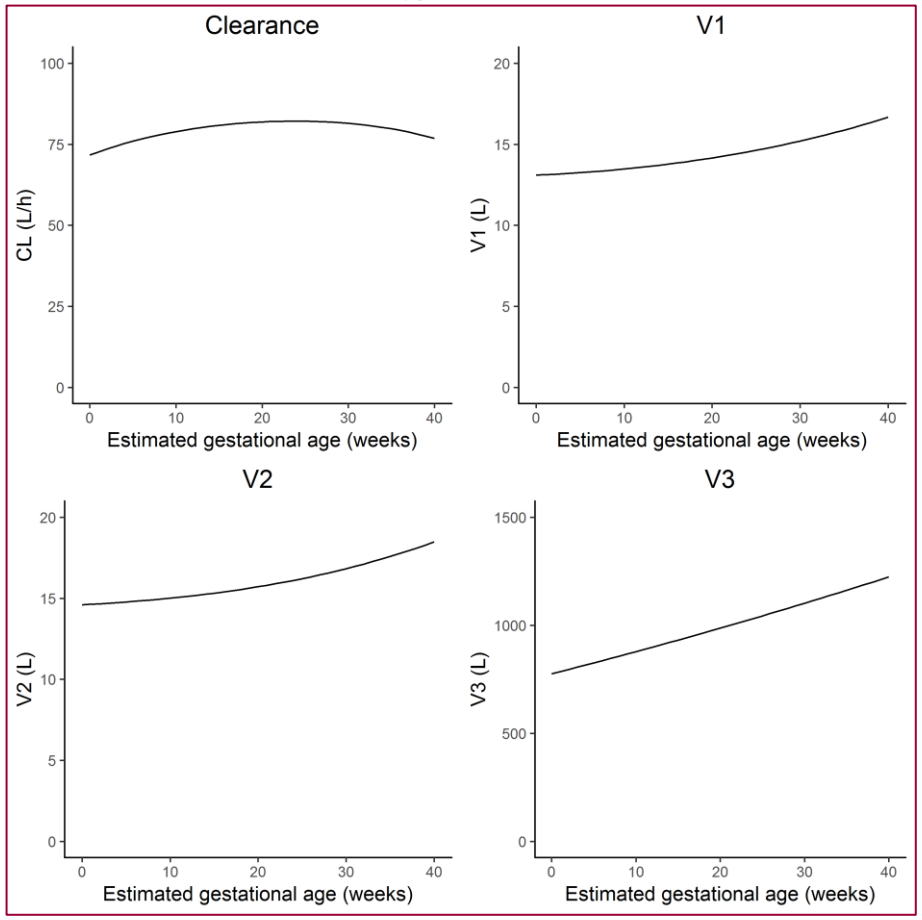
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Anthracyclines

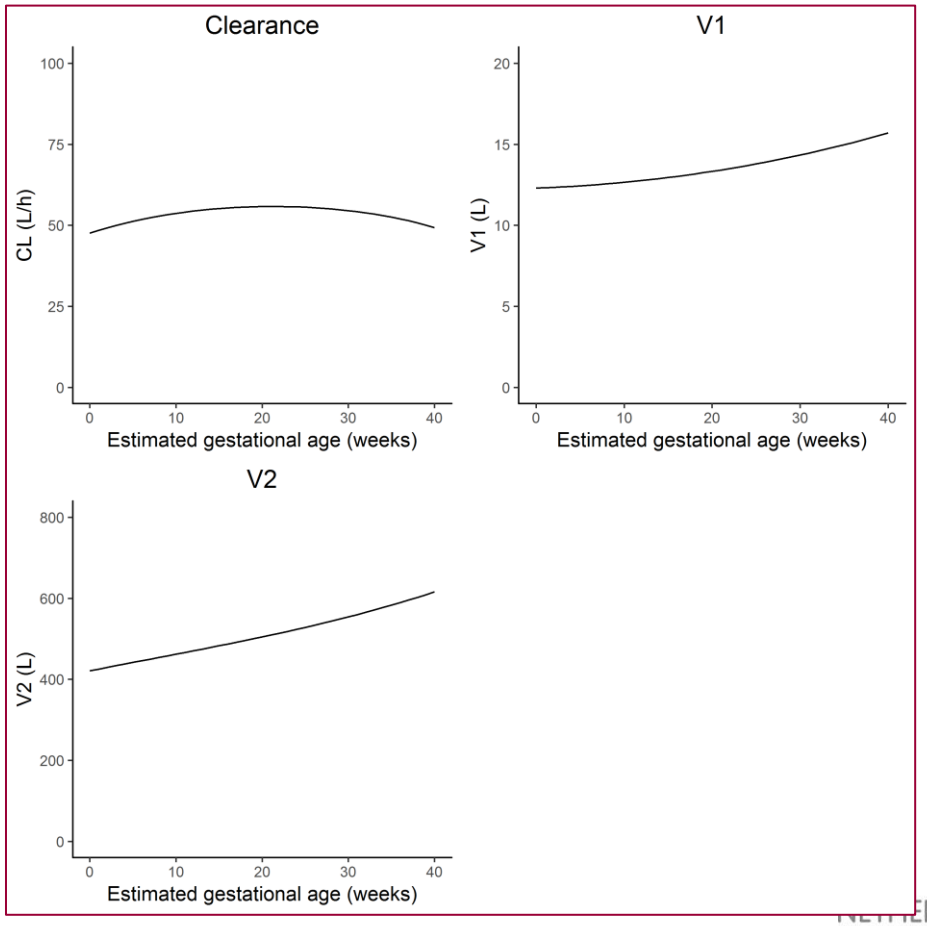
	Epirubicin	Doxorubicin
Absorption	i.v. administration	i.v. administration
Distribution	f_u = 0.23 (albumin ↓) Large volumes of distribution ↑	f_u = 0.25 (albumin ↓) Large volumes of distribution ↑
Metabolism	CYP3A4 ↑ UGTB7	CYP3A4 ↑
Excretion	f_u = 0.1	f_u = 0.05
		

Typical gestational change in parameters

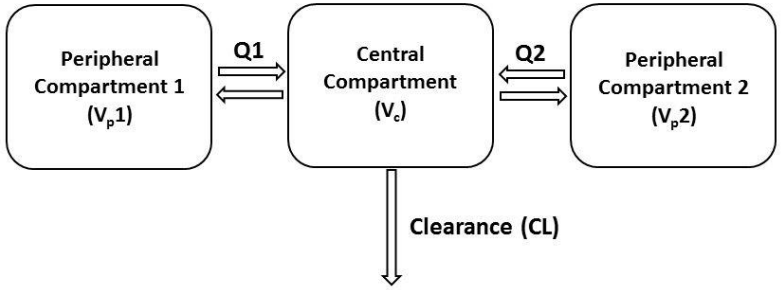
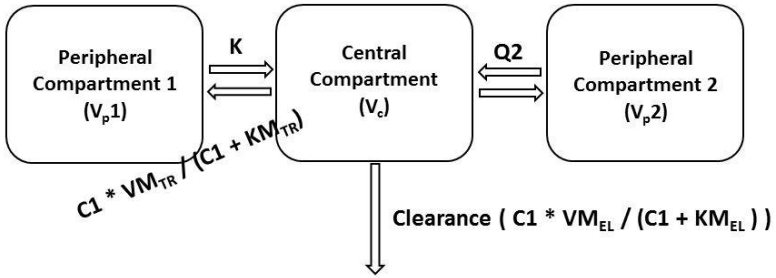
Epirubicin



Doxorubicin



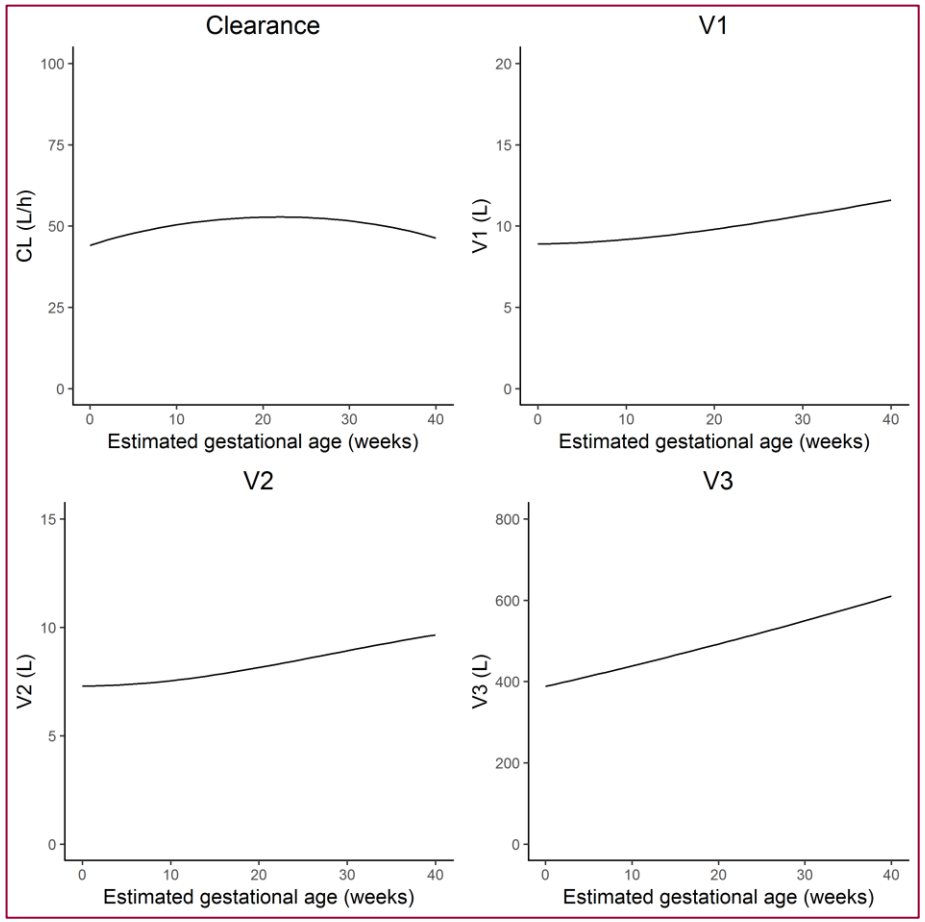
Taxanes

	Docetaxel	Paclitaxel
Absorption	i.v. administration	i.v. administration
Distribution	f_u = 0.06 (alpha-1-glycoprotein ↓) Large volumes of distribution ↑	f_u = 0.05 (albumin ↓) Large volumes of distribution ↑
Metabolism	CYP3A4 ↑ CYP3A5	CYP3A4 ↑ CYP2C8
Excretion	f_u = 0.06	f_u = 0.06
		

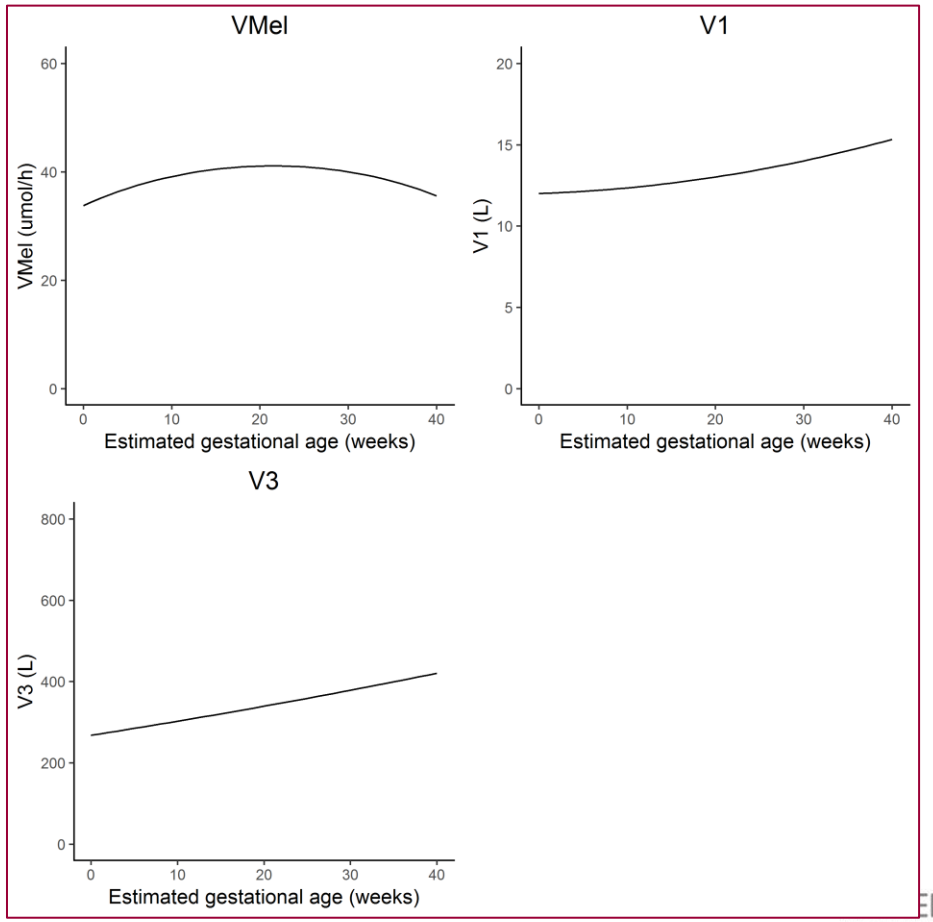
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Typical gestational change in parameters

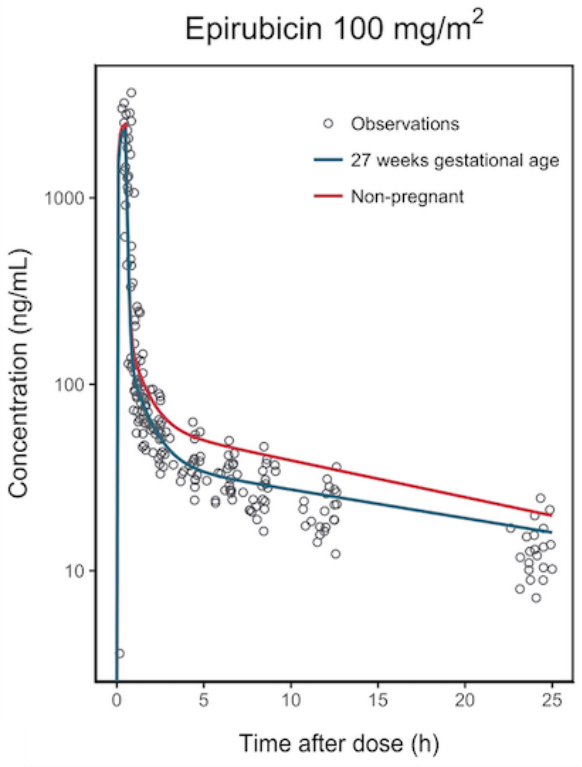
Docetaxel



Paclitaxel

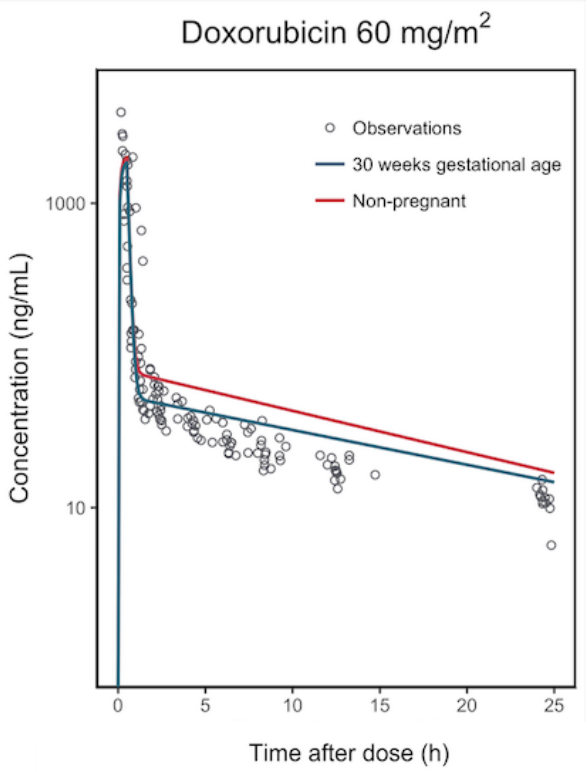


Application:
External evaluation



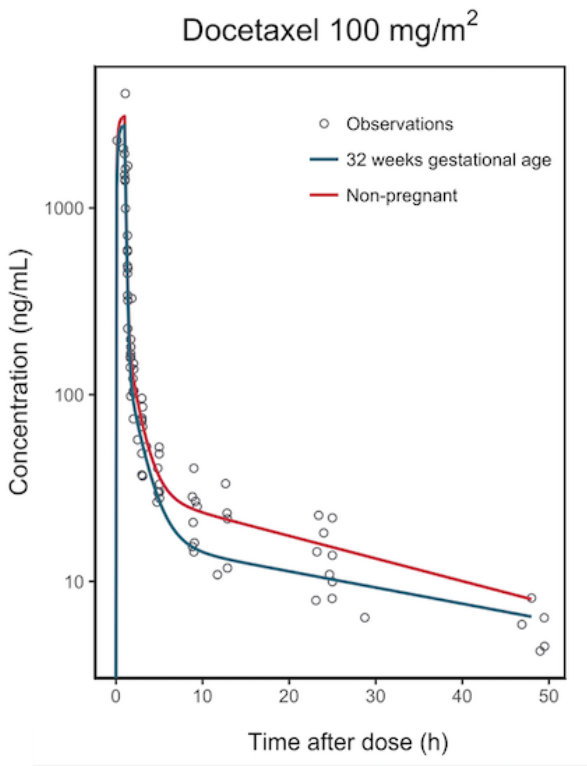
n = 16

ΔOFV=-148



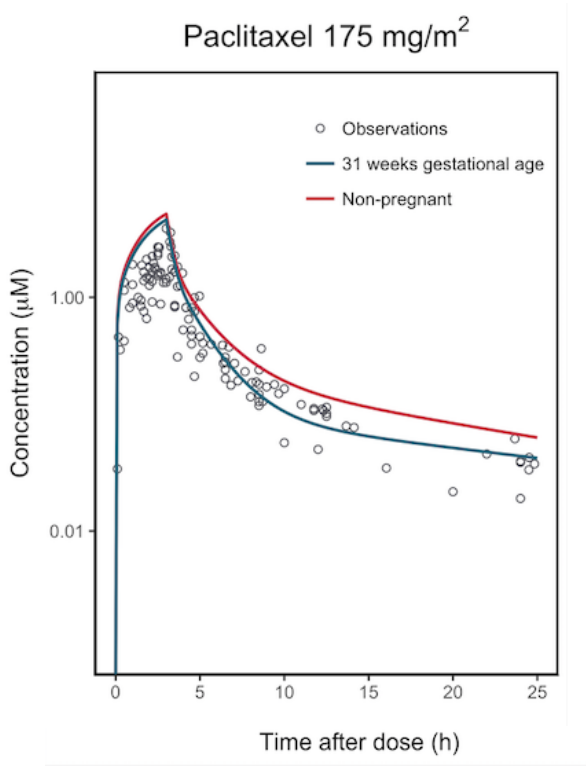
n = 22

ΔOFV=-62.2



n = 9

ΔOFV=-4.66



n = 20

ΔOFV=-18.4

Summary

- Framework provides an adequate description of the PK in pregnant women
- Addition of pregnant physiology improves model predictions
- Clinical relevance difficult to assess
- Method may be used for extrapolation purposes to predict dosing regimens in pregnant women for drugs for which PK data from pregnant women are unavailable

Acknowledgements

Netherlands Cancer Institute
Thomas Dorlo
Alwin Huitema
Frédéric Amant
Jos Beijnen
Hilde Rosing
Bas Thijssen

Leiden Academic Centre for Drug Research
Coen van Hasselt

UZ Leuven
Kristel van Calsteren
Katrien van Tornhout
Charlotte Maggen

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK