



Semi-physiological Enriched Population Pharmacokinetic Modelling to Predict the Effects of Pregnancy on the Pharmacokinetics of Cytotoxic Drugs

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Abstract

Background and Objective As a result of changes in physiology during pregnancy, the pharmacokinetics (PK) of drugs can be altered. It is unclear whether under- or overexposure occurs in pregnant cancer patients and thus also whether adjustments in dosing regimens are required. Given the severity of the malignant disease and the potentially high impact on both the mother and child, there is a high unmet medical need for adequate and tolerable treatment of this patient population. We aimed to develop and evaluate a semi-physiological enriched model that incorporates physiological changes during pregnancy into available population PK models developed from non-pregnant patient data.

Methods Gestational changes in plasma protein levels, renal function, hepatic function, plasma volume, extracellular water and total body water were implemented in existing empirical PK models for docetaxel, paclitaxel, epirubicin and doxorubicin. These models were used to predict PK profiles for pregnant patients, which were compared with observed data obtained from pregnant patients.

Results The observed PK profiles were well described by the model. For docetaxel, paclitaxel and doxorubicin, an over-prediction of the lower concentrations was observed, most likely as a result of a lack of data on the gestational changes in metabolizing enzymes. For paclitaxel, epirubicin and doxorubicin, the semi-physiological enriched model performed better in predicting PK in pregnant patients compared with a model that was not adjusted for pregnancy-induced changes.

Conclusion By incorporating gestational changes into existing population pharmacokinetic models, it is possible to adequately predict plasma concentrations of drugs in pregnant patients which may inform dose adjustments in this population.

Key Points

As a result of short-term fetal and maternal safety data, chemotherapy is increasingly used to treat pregnant patients with cancer. As pregnant patients are typically excluded from clinical trials, there is a high unmet medical need for adequate and tolerable dosing regimens in this patient population. By incorporating gestational changes into existing population pharmacokinetic models, it is possible to adequately predict plasma concentrations of drugs in pregnant patients which may inform dose adjustments in this population.

1 Introduction

Cancer is manifested in one out of 1000 pregnancies. Recently, it has been shown that oncological treatment during pregnancy, under strict guidelines and precautions, is safe and thus recommended [1]. An increased use of chemotherapy during pregnancy has been associated with an increased number of live births. Nevertheless, as pregnant patients are typically excluded from clinical trials and post-marketing studies in pregnant patients are rarely performed, information on the appropriateness of dosing strategies during pregnancy is missing [2].

During pregnancy, pharmacokinetics (PK) of drugs can be altered as a result of various changes in several physiological processes. Over the past years, efforts have been made to quantify these physiological alterations during pregnancy [3, 4]. Firstly, a gradual decrease in plasma levels for both albumin and α 1-acid-glycoprotein over the

course of pregnancy has been reported. Furthermore, it has been shown that the glomerular filtration rate (GFR) increases until the third trimester but then slightly decreases again during late pregnancy. A 1.5-fold increase in total body water during pregnancy has been shown, as well as an increase in body fat, which may result in alterations in distribution volumes. Nevertheless, for other parameters, such as drug metabolizing enzymes, limited and, on occasion, conflicting data exist. These changes may result in increased or decreased drug concentrations compared with non-pregnant women, and this may change over the course of pregnancy [3].

Given the small therapeutic window of most cytotoxic drugs, small changes in concentrations of cytotoxic agents may influence the therapeutic effect. A major concern is that lower drug plasma concentrations in pregnant women might result in a negative effect on survival. However, results from small cohorts of pregnant patients with breast cancer, cervical cancer and Hodgkin lymphoma have shown that cancer prognoses are similar to those of non-pregnant patients [5–7].

An empirical PK analysis of four cytotoxic agents obtained from pregnant cancer patients indeed showed alterations in PK parameter estimates compared with non-pregnant patients [8]. Given the complexity of the physiological changes during pregnancy, the magnitude and relevance of these alterations on the PK of anticancer drugs is not straightforward. Ideally, PK studies should be performed to quantify these changes. However, clinical studies in pregnant women are difficult to perform as a result of the low incidence of malignancies in women of child-bearing potential, and the many variables that should be taken into account [gestational age, cancer (sub)type, treatment regimen, co-medication] [9]. Nevertheless, there is a high unmet medical need for adequate and tolerable treatment of this neglected patient population.

Whole-body physiologically based PK models can be used to predict pregnancy-induced changes in PK [10]. However, for most cytotoxic agents, extensive knowledge on the PK of the drug in non-pregnant patients is available mostly in the form of empirical population PK models. With this work, we aimed to develop a methodology in which the advantages of physiologically based PK models are combined with relevant existing knowledge of the PK in non-pregnant patients, enabling the prediction of individual PK profiles of a range of cytotoxic drugs in pregnant patients. To this end, we implemented a semi-physiological enriched pregnancy model including changes over the gestational time that allows the prediction of the PK of cytotoxic drugs in pregnant women using only available empirical compartmental models based on non-pregnant patient PK data. To evaluate the physiologically enriched model, we used PK data from pregnant women who were treated with either

doxorubicin, epirubicin, docetaxel or paclitaxel, collected internationally over the course of 10 years.

2 Methods

2.1 Development of a Semi-physiological Enriched Model

Physiological changes over time during the course of pregnancy have extensively been described in the literature [3, 4]. To describe the typical change in PK parameters during pregnancy, a selection of relevant empirical equations for physiological changes from Abduljalil et al. were implemented in our semi-physiological predictions [3]. This work includes all relevant physiological parameters that might have an influence on the PK of either doxorubicin, epirubicin, docetaxel or paclitaxel.

2.1.1 Plasma Proteins

Plasma protein levels, such as albumin and alpha1-acid glycoprotein (AAG), decrease during pregnancy, which may affect the unbound concentration of drugs that are highly protein bound. The unbound plasma concentration affects the pharmacological effect of the drug and it is mostly the unbound drug fraction that is renally or hepatically eliminated [3]. The following empirical equations describe the serum albumin concentration (C_{alb}) (Eq. 1) and serum AAG concentration (C_{AAG}) (Eq. 2) as a function of estimated gestational age (EGA):

$$C_{\text{alb}}(\text{EGA}) \left[\frac{\text{g}}{\text{L}} \right] = 45.8 - 0.177 \text{ EGA} - 0.0033 \text{ EGA}^2 \quad (1)$$

$$C_{\text{AAG}}(\text{EGA}) \left[\frac{\text{g}}{\text{L}} \right] = 0.74 - 0.0088 \text{ EGA} + 0.0001 \text{ EGA}^2. \quad (2)$$

To determine the change in unbound drug concentration (f_u) over time during pregnancy, the dissociation constant (k_D) was calculated by Eq. (3) and assumed to remain constant during the complete pregnancy period. Subsequently, Eq. (4) was used to determine the expected change in free unbound drug fraction during pregnancy, for which it was assumed that the free drug concentrations are much lower than k_D and that the maximal binding capacity per protein molecule is 1. This would imply linear protein binding and thus an f_u independent of the free drug concentration.

$$k_D = \left(\frac{C_{\text{protein}}(\text{EGA} = 0) \times f_u(\text{EGA} = 0)}{1 - f_u(\text{EGA} = 0)} \right) \quad (3)$$

$$f_u = \frac{1}{\left(1 + \frac{C_{\text{protein}}(\text{EGA})}{k_D}\right)}, \quad (4)$$

where C_{protein} is either C_{alb} or C_{AAG} as derived from Eqs. (1) or (2). Previously established drug-specific non-pregnant (i.e. EGA = 0 weeks) percentage of protein binding was used for f_u (EGA = 0) (Table 1).

2.1.2 Clearance

Clearance can be subdivided into the two main routes, renal (CL_R) and hepatic (CL_H) clearance as follows:

$$CL(\text{EGA}) = CL_R(\text{EGA}) + CL_H(\text{EGA}). \quad (5)$$

Many changes occur in the urinary and hepatic system during pregnancy, including an increase in GFR, enhanced creatinine clearance (CL_{CR}) and hepatic blood flow ($Q_{H,\text{blood}}$). Also, variable changes in activities of drug-metabolizing enzymes have been reported. Since all four studied drugs are at least partially eliminated by glomerular filtration and only the unbound drug fraction is eliminated, the change in renal clearance during pregnancy was defined by Eq. (6), in which GFR was described by Eq. (7) and $CL_R(\text{EGA} = 0)$ is the reported renal clearance in non-pregnant patients.

$$CL_R(\text{EGA}) = CL_R(\text{EGA} = 0) \times \frac{\text{GFR}(\text{EGA})}{\text{GFR}(\text{EGA} = 0)} \times \frac{f_u(\text{EGA})}{f_u(\text{EGA} = 0)} \quad (6)$$

$$\text{GFR}(\text{EGA}) \left[\frac{\text{mL}}{\text{min}} \right] = 114 + 3.236 \text{ EGA} - 0.0572 \text{ EGA}^2. \quad (7)$$

Limited and contradictory data are reported on the change in $Q_{H,\text{blood}}$ during pregnancy, we therefore assumed that the hepatic blood flow remained unchanged over pregnancy and was thus fixed to a typical non-pregnant value of 109 L/h [11]. Both changes in unbound fraction and changes in $Q_{H,\text{plasma}}$ which change during pregnancy can influence CL_H . A decrease in haematocrit (HCT) is observed during pregnancy, which is described by Eq. (8):

$$\text{HCT}(\text{EGA}) [\%] = 39.1 - 0.054 \text{ EGA} - 0.0098 \text{ EGA}^2. \quad (8)$$

Subsequently, the hepatic plasma flow ($Q_{H,\text{plasma}}$) can be described with Eq. (9):

$$Q_{H,\text{plasma}}(\text{EGA}) [\text{L/h}] = \left(1 - \left(\frac{\text{HCT}_{\text{EGA}}}{100}\right)\right) \times Q_{H,\text{blood}}. \quad (9)$$

To describe the relationship between CL_H , the changing fraction unbound, the hepatic plasma flow ($Q_{H,\text{plasma}}$) and

Table 1 PK characteristics of the included drugs and non-pregnant population PK models.

	Docetaxel ^a	Paclitaxel ^b	Epirubicin ^c	Doxorubicin ^d
Protein binding (%)	94	95	77	75
Metabolism	CYP3A4	CYP3A4 CYP2C8	CYP3A4 UGT2B7	CYP3A4
CL_R (%)	6	6	10	5
Non-pregnant PK model ^e	CL = 44.1 L/h (29.4%) V1 = 8.9 L (37.8%) Q1 = 6.1 L/h V2 = 7.3 L Q2 = 14.4 L/h (20.3%) V3 = 388 L	V1 = 12 L V3 = 268 L (36.2%) VM _{EL} = 33.8 μmol/h (27.0%) KM _{EL} = 0.44 μmol/L VM _{TR} = 177 μmol/h (26.7%) KM _{TR} = 1.61 μmol/L (66.0%) K ₂₁ = 1.21 h ⁻¹ Q2 = 16.8 L/h (49.5%)	CL = 71.7 L/h (15%) V1 = 13.1 L Q1 = 70.6 L/h V2 = 776 L Q2 = 17.8 L/h V3 = 14.6 L	CL = 47.6 L/h (24.6%) V1 = 12.3 L (11.8%) Q1 = 60.3 L/h (20.7%) V2 = 421 L (25.0%)

V1 volume of central compartment, V2 volume of first peripheral compartment, V3 volume of second peripheral compartment, CL clearance, Q1 inter-compartmental clearance between central and first peripheral compartment, Q2 inter-compartmental clearance between central and second peripheral compartment, VM_{EL} maximal elimination rate, KM_{EL} plasma concentration at half VM_{EL}, VM_{TR} maximal transport rate from the central to the first peripheral compartment (paclitaxel), KM_{TR} plasma concentration at half VM_{TR}, K₂₁ rate constant from the first peripheral compartment to the central compartment (paclitaxel)

^a[15]

^b[16]

^c[18]

^d[17]

^eParameter estimates from base model [inter-individual variability, expressed as percentage coefficient of variation (CV%)]

intrinsic clearance (CL_{int}), the following well-stirred liver model equation was used:

$$CL_H(EGA) = \left(\frac{Q_{H,plasma}(EGA) \times CL_{int}(EGA) \times f_u(EGA)}{Q_{H,plasma}(EGA) + CL_{int}(EGA) \times f_u(EGA)} \right). \quad (10)$$

Equation (10) was rearranged to determine the CL_{int} in non-pregnant patients, using previously estimated drug-specific values of CL_H (Eq. 11).

$$CL_{int}(EGA = 0)[L/h] = - \left(\frac{CL_H(EGA = 0) \times Q_{H,plasma}(EGA = 0)}{CL_H(EGA = 0) \times f_u(EGA = 0) - Q_{H,plasma}(EGA = 0) \times f_u(EGA = 0)} \right). \quad (11)$$

To account for the changes in activities of enzymatic pathways during pregnancy, CL_{int} was corrected for the change in enzyme activity (E):

$$CL_{int}(EGA)[L/h] = CL_{int}(EGA = 0) \times \frac{E(EGA)}{E(EGA = 0)}, \quad (12)$$

where $E(EGA)$ represents the enzyme activities of relevant enzymes during pregnancy, and $EGA = 0$ is the enzyme activity in the non-pregnant state (i.e. 100%). The change in drug-metabolizing enzyme activity of CYP3A4 was described as follows:

$$CYP3A4activity(EGA)[\%] = 100 + 2.9826 EGA - 0.0741 EGA^2. \quad (13)$$

Although the activity of CYP2C8 and UGT2B7 might be increased during pregnancy, little is known about the magnitude of this increase [3]. We therefore assumed that the activity of these enzymes remained unchanged over pregnancy.

2.1.3 Volume of Distribution

We used the relationship between distribution volume (V_d), plasma volume (V_{plasma}) and a drug-specific metric for total body fluids (V_E) minus V_{plasma} , as previously proposed by Gibaldi and McNamara [12]:

$$V_d(EGA)[L] = V_{plasma}(EGA) + [V_E(EGA) - V_{plasma}(EGA)] \frac{f_u}{f_t}, \quad (14)$$

where f_u is the fraction of unbound drug in plasma as described in Eq. (4), f_t is the unbound drug fraction in tissue and f_u/f_t represents the tissue partition coefficient. f_u/f_t was assumed to remain constant during pregnancy since it is expected that the change in plasma proteins affects f_u and f_t to a similar extent. An increase in V_{plasma} is observed during pregnancy, which is described by Eq. (15):

$$V_{plasma}(EGA)[L] = 2.5 - 0.0223 EGA + 0.0042 EGA^2 - 0.00007 EGA^3. \quad (15)$$

Apparent volumes of distribution were expected to change during pregnancy. Reported non-pregnant volumes of distribution were scaled to the pregnant state using Eqs. (14–16). V_d is the volume of distribution of interest and V_E is represented by either total body water (TBW) or extracellular water (ECW), depending on the extent of the volumes of distribution:

$$TBW(EGA)[L] = 31.67 + 0.275 EGA + 0.0024 EGA^2 \quad (16)$$

$$ECW(EGA)[L] = 11.86 + 0.0187 EGA + 0.0016 EGA^2. \quad (17)$$

2.2 Prediction

Pharmacokinetic data for doxorubicin, epirubicin, docetaxel and paclitaxel were available from a prospective multinational and multicentre clinical study investigating the effects of the administration of chemotherapy during pregnancy. Pharmacokinetic and clinical results from this trial were reported previously [1, 8]. Concentration–time curves from 26, 16, 9 and 19 pregnant patients were available for doxorubicin, epirubicin, docetaxel and paclitaxel, respectively.

We searched the literature to obtain non-linear mixed-effects population PK models that adequately described the PK of the four cytotoxic drugs in non-pregnant patients [13–16]. These models were extended with the above described semi-physiological gestational changes to provide PK predictions for pregnant individuals. Covariates were excluded from the predictions to predict the typical change in PK parameters during pregnancy. Drug-specific PK characteristics that were taken into account, such as protein binding and routes of metabolism, are presented in Table 1. With these PK parameters, typical concentration–time profiles were predicted for EGAs that matched the observed dataset. To provide a valid comparison to the observed concentration–time profiles, the dosing regimens from the clinical data were used. Since dosing of doxorubicin, epirubicin, docetaxel and paclitaxel is based on a patients' body surface area (BSA), the median BSA found in the studied patients was used (Table 2).

2.3 Evaluation

The observed concentration–time profiles available from the clinical study were used to visually evaluate the performance

of the semi-physiological enriched models. Secondly, individual model fits and predictions were obtained for the observed pharmacokinetic data from pregnant women based on individual Bayesian estimates which were obtained by using non-linear mixed-effects modelling, more specifically by using the MAXEVAL = 0 and POSTHOC options in NONMEM® [17]. The fit of the semi-physiological model during pregnancy was compared to the fit of the model parameters for the non-pregnant state (EGA = 0). Subsequently, changes in the objective function value (Δ OFV, corresponding to minus twice the log-likelihood) were evaluated to compare and assess both models.

2.4 Software

Predictions were performed using a differential equation system in R (version 4.2.1) together with the R package deSolve [18]. NONMEM® v.7.5 (ICON Development Solutions, Ellicott City, MD, USA) was used to evaluate the developed model [17].

3 Results

3.1 Docetaxel

The PK of intravenously administered docetaxel has adequately been described by a linear three-compartment model with linear elimination [13]. Docetaxel is mainly metabolized by CYP3A4 and thereafter eliminated as inactive metabolites in the faeces. Hence, the change in CYP3A4 enzyme activity during pregnancy was incorporated in the predictions. As docetaxel is mainly bound to AAG in the plasma, Eq. (2) was incorporated to account for protein binding. Tables 3 and 4 show the typical change in the docetaxel primary and secondary PK parameters, respectively, during pregnancy. The largest increase for the primary PK parameters was observed for V3 in the third trimester. However, the largest effect in secondary parameter was observed for AUC_{0-48h} in the second and third trimester, suggesting that change in CL is more clinically relevant than in V3.

Typical concentration–time curves were predicted for the median gestational age (GA), which was 32 weeks for the patients treated with docetaxel. Although trough concentrations were slightly overpredicted, the typical observed pregnant concentrations were well described by the semi-physiological enriched model (Fig. 1). Additionally, the predictions clearly demonstrated that the use of non-pregnant parameter estimates resulted in an overprediction of the observed concentrations (Fig. 1). Comparison of the model fit for the individual predictions based on the semi-physiological pregnant parameter estimates versus non-pregnant parameter estimates resulted in an increase in OFV of 70.1 points.

Table 3 Typical gestational changes in PK parameters of semi-physiological model by trimester compared with non-pregnant

	Docetaxel	Paclitaxel	Doxorubicin	Epirubicin
EGA 12 weeks				
CL (L/h)	+ 15.4%	–	+ 10.4%	+ 5.24%
VM _{EL} (μmol/h)	–	+ 16.6%	–	–
V1 (L)	+ 4.26%	+ 3.82%	+ 3.79%	+ 3.71%
V2 (L)	+ 4.63%	–	+ 11.7%	+ 3.59%
V3 (L)	+ 15.7%	+ 15.6%	–	+ 15.9%
EGA 28 weeks				
CL (L/h)	+ 24.0%	–	+ 16.8%	+ 11.4%
VM _{EL} (μmol/h)	–	+ 26.7%	–	–
V1 (L)	+ 17.7%	+ 14.9%	+ 14.7%	+ 14.2%
V2 (L)	+ 20.0%	–	+ 29.1%	+ 13.5%
V3 (L)	+ 38.6%	+ 38.3%	–	+ 39.0%
EGA 40 weeks				
CL (L/h)	+ 20.6%	–	+ 16.0%	+ 15.4%
VM _{EL} (μmol/h)	–	+ 24.9%	–	–
V1 (L)	+ 30.2%	+ 27.8%	+ 27.6%	+ 27.2%
V2 (L)	+ 32.2%	–	+ 46.3%	+ 26.6%
V3 (L)	+ 57.3%	+ 56.9%	–	+ 57.7%

Table 2 Patient characteristics PK study

	Docetaxel ^a	Paclitaxel ^a	Epirubicin ^a	Doxorubicin ^a
Total patients, <i>n</i>	9	20	16	22
Total cycles, <i>n</i>	10	25	22	27
EGA (weeks) [median (range)]	31.8 (26.1–35.0)	31.0 (16.7–35.7)	26.8 (19.0–34.0)	28.7 (15.0–36.3)
BSA (m ²) [median (range)]	1.91 (1.66–2.06)	1.92 (1.74–2.27)	1.89 (1.58–2.48)	1.78 (1.56–2.49)
Dosing schedule	100 mg/m ²	60 mg/m ² 80 mg/m ² 175 mg/m ²	100 mg/m ²	25 mg/m ² 50 mg/m ² 60 mg/m ²

^a[1, 8]

Table 4 Typical gestational changes in secondary PK parameters of semi-physiological model by trimester compared with non-pregnant

	Docetaxel (%)	Paclitaxel (%)	Doxorubicin (%)	Epirubicin (%)
EGA 12 weeks				
AUC _{0–48h}	– 13.5	– 3.41	– 9.74	– 1.98
C _{max}	– 10.1	– 2.46	– 4.69	+ 1.28
EGA 28 weeks				
AUC _{0–48h}	– 20.3	– 7.66	– 15.6	– 4.41
C _{max}	– 15.2	– 10.7	– 7.80	+ 2.71
EGA 40 weeks				
AUC _{0–48h}	– 19.1	– 11.8	– 16.4	– 6.08
C _{max}	– 13.8	– 14.0	– 8.52	+ 0.49

3.2 Paclitaxel

For paclitaxel, a population PK model that consists of a three-compartment model with saturable distribution to the first peripheral compartment and saturable clearance for the central compartment has been published [14]. Paclitaxel is mainly bound to albumin in plasma, metabolized by both CYP3A4 and CYP2C8, and partly eliminated by the faeces. Hence, the change in albumin plasma levels and CYP3A4 enzyme activity were used. Data on the gestational change in CYP2C8 activity are still lacking and could therefore not be included. To account for the change in clearance of paclitaxel during pregnancy, the maximal elimination rate (VM_{EL}) was scaled according to Eqs. (10–13). Typical parameter changes were similar to the changes that were observed for docetaxel. All volumes of distribution increased during pregnancy, with a maximum increase of approximately 60% for V3. Secondary PK parameters were mainly affected in both the second and third trimester, with a predicted decrease of approximately 10%. Concentration–time curves were predicted for the median GA of 31 weeks that was observed in the evaluation dataset (Fig. 1). The semi-physiological predictions adequately described the observed paclitaxel concentrations. A minor overprediction of the observed concentrations between pre-dose and 5 h after administration was observed. Notwithstanding, an overprediction of the observations was evident when non-pregnant estimates were used, especially in the elimination phase of the concentration–time curve. The model fit for the individual predictions based on the semi-physiological pregnant parameter estimates showed decrease of the OFV of 279.3 compared with non-pregnant parameter estimates.

3.3 Doxorubicin

The PK of doxorubicin has previously been described by a two-compartment model with linear clearance and extensive distribution (Table 1) [15]. Doxorubicin is metabolized by

CYP3A4 into both active and inactive metabolites, which are mainly excreted by the faeces. Small initial increases ranging from 3.8 to 10.4% were observed for CL and V1. The largest increase was observed for V2, which increased by 46.3% in the third trimester. However, just as for docetaxel the largest clinically relevant decrease in secondary PK parameters was the AUC_{0–48h} in the second and third trimester.

Typical concentration–time curves were predicted for the median GA, which was 29 weeks for the patients treated with doxorubicin. Although doxorubicin concentrations were still slightly overpredicted in the terminal elimination phase, this overprediction was smaller than for the non-pregnant model-based predictions and concentrations were well described in the initial part of the elimination phase until about 5 h after administration.

Figure 1 clearly demonstrates that predictions using model parameters based on the non-pregnant state resulted in an overprediction of the observed doxorubicin concentrations. In addition, the model fit for the individual predictions based on the semi-physiological pregnant parameter estimates showed a decrease of the OFV of 74.0 compared with non-pregnant parameter estimates.

3.4 Epirubicin

For epirubicin, a three-compartment model with linear clearance and extensive tissue distribution has been published [16]. Epirubicin is metabolized by CYP3A4, glucuronidated and thereafter excreted by the faeces. For epirubicin, typical parameter increases in CL and V1 were comparable with the observed increases in doxorubicin CL and V1. However, V2 and V3 showed a larger increase than was observed for doxorubicin V2. Secondary PK parameters were hardly affected, with the largest decrease in AUC_{0–48h} in the third trimester of 6.08%. Concentration–time curves were predicted for the median observed GA of 27 weeks. The semi-physiological enriched model adequately predicted the epirubicin concentration–time curves that were observed during

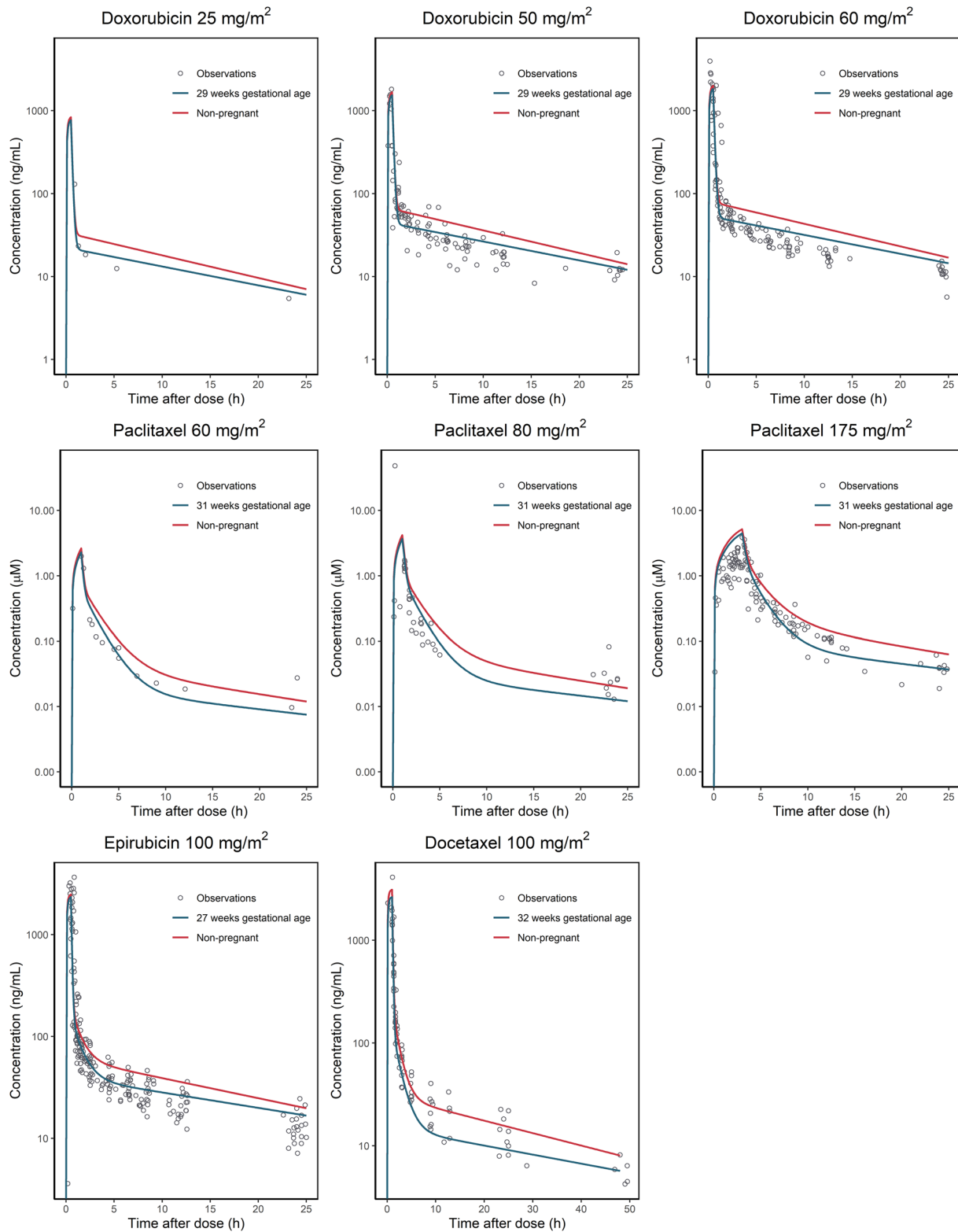


Fig. 1 Predicted concentration-time profiles of docetaxel, paclitaxel, doxorubicin and epirubicin for non-pregnant (red lines) and pregnant (blue lines) patients. Grey open dots represent the observations of pregnant patients only

pregnancy. Additionally, the predictions using non-pregnant estimates showed an overprediction of the observed concentration–time curve. Comparison of the model fit for the individual predictions based on the non-pregnant versus the semi-physiological pregnant parameter estimates showed a significantly improved fit for the latter, with a decrease in OFV of 21.2 points observed for epirubicin.

4 Discussion

With this work, we have demonstrated the feasibility and relevance of a semi-physiological prediction approach in which prior knowledge of both the human population PK of a cytotoxic drug and physiological changes during pregnancy are combined to predict changes in PK in pregnant patients. To this end, we used the physiological alterations during pregnancy that have been described in a quantitative manner by Abduljalil et al. [3].

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) provided guidance on the use of medicinal products during pregnancy [2, 19, 20]. In these guidelines, it is stated that post-marketing studies should be performed and exposure registries should be established for drugs that are used in women of child-bearing age. With these studies, data on the outcomes of pregnancies exposed to these drugs are collected. The EMA additionally advises to use a population PK approach to identify potential gestational effects and hence simulate doses that achieve PK exposure in pregnant patients similar to non-pregnant patients.

An alternative widely used approach is the development of a full physiologically based pharmacokinetic model. These models are constructed from known anatomical and physiological characteristics (system-related parameters) combined with physicochemical and clinical pharmacological drug characteristics (drug-related parameters). With these models, extrapolation to unstudied conditions can be made e.g. for drug–drug interactions, use of drugs in children or in pregnant patients. However, when drugs are introduced for the treatment of pregnant patients, clinical information on the drug's disposition and elimination in non-pregnant patients is generally already available in the form of empirical population PK models and can be of great value to inform the extrapolation to pregnant patients. The here-presented semi-physiological enriched model implements a hybrid methodology that integrates actual patient data with the quantitative and longitudinal physiological changes during pregnancy. This latter aspect is comparable to the use of system-related parameters in physiologically based pharmacokinetic models. This provides a first prediction of the PK profile in pregnant women based on their GA, taking into account established non-pregnant empirical

PK models. This is particularly relevant for cytotoxic agents as their application in pregnant cancer patients is rare and difficult due to their mutagenic and teratogenic potential, but nevertheless optimal treatment is sometimes required for maternal survival [1].

For docetaxel, the semi-physiological approach did not perform better than the non-pregnant PK model parameters and only modest changes in typical parameters were observed. This shows that pregnancy has a limited effect on the PK of docetaxel and predictions using the parameters based on non-pregnant data perform well for the pregnant population. In an empirical population PK analysis, we found small changes in docetaxel PK during pregnancy as well. For the paclitaxel 80 mg/m² dose regimen, the predictions showed an overprediction of the concentrations. This could be explained by the very small sample size and wide gestational age range in the pregnancy dataset that was available for evaluation. In addition to CYP3A4, paclitaxel is metabolized by CYP2C8, for which no relationship with gestational age is available due to a lack of data on the dynamics of this enzyme. An underestimation of the CYP2C8 activity during pregnancy could in theory be a potential cause for the observed overprediction. Furthermore, the PK of taxanes is characterized by large inter-individual variability which complicates the identifiability of an effect of gestation in a small sample size. The predicted epirubicin concentrations were in good agreement with the observations, although some overprediction of the trough concentrations was observed. Epirubicin is metabolized by both CYP3A4 and UGT2B7. For UGT2B7 increased activity during pregnancy has been reported but this has not been quantified [3]. The assumption of unchanged UGT2B7 activity during pregnancy could fairly result in an underprediction of the clearance of epirubicin. For doxorubicin, we used a previously described two-compartment model that was developed using sparsely collected PK data. Predictions with this non-pregnant model for the pregnant population resulted in an overprediction of the observed concentrations in the terminal elimination phase. The observed, rich-sampled data indicate that a three-compartment model might be better suitable to describe doxorubicin PK. Nevertheless, the semi-physiological approach performed significantly better than the model-based predictions based on non-pregnant parameter estimates. Overall, our semi-physiological enriched model provided a reasonable prediction of the PK in women at any stage of gestation for various cytotoxic drugs. In line with previous findings, lower drug concentrations were predicted during pregnancy compared with the non-pregnant state, and therefore, clinical implications described previously also apply here [21]. Moreover, the semi-physiological model resulted in a significant better fit of the PK data from pregnant patients than the literature-based models for paclitaxel, epirubicin and doxorubicin.

This semi-physiological enriched model is depending on assumptions and simplifications which might all pose limitations. Firstly, we only accounted for changes in maternal PK and did not include changes related to the foetal compartment. It has been shown that the placenta is a good protector for taxanes and anthracyclines. In animal studies, foetal paclitaxel plasma concentrations were approximately 1% of the maternal concentrations while foetal plasma docetaxel levels were not detectable. In addition, placental passage was 4% for epirubicin and 8% for doxorubicin [9]. This suggests limited distribution to the foetal compartment of the here-investigated chemotherapeutics. However, the semi-physiological based model could easily be extended with a foetal compartment for drugs that cross the placenta. Consequently, foetal exposure can be predicted, based on the predicted maternal PK. Secondly, we did not incorporate changes in transporters and their possible implications on clearance. Transporters that could be explored in further updates of the model are P-gp and OATP1B3, of which docetaxel and paclitaxel are known substrates. Also, to extend our model to other drugs with other key disposition determinants than described in our model (such as transporters), first a relation between gestational age and key disposition determinants in the form of an empirical equation has to be available before it can be implemented. Thirdly, we assumed unchanged partition coefficients that account for the distribution between body compartments. As the proportion of body fat shows a typical increase in addition to alterations in body fluids, this assumption might lead to an underprediction of the pregnant volumes of distribution. The hepatic blood flow was also assumed to remain constant during pregnancy. Contradictory results have been published regarding the change in hepatic blood flow during pregnancy. In these studies, different measurement methods were applied resulting in highly variable and inconsistent results. In addition, the relationship between the gestational induced change in other cardiovascular parameters such as cardiac output and the hepatic blood flow remains unclear [3]. Hence, the change in hepatic clearance during pregnancy was driven by the change in metabolizing enzyme activity. A maternal increase in CYP3A4 activity has been shown in several studies and was, therefore, included in our semi-physiological enriched model. The activity of UGT2B7 has been suggested to increase over pregnancy as well, but the magnitude of this increase is still not quantitatively described [3]. Changes in CYP2C8 could not be incorporated because no relationships with gestation have been established. Consequently, non-pregnant metabolizing activity was assumed for these enzymes over pregnancy. Also, it should be noted that the developed semi-physiological model relies on the validity and accuracy of the estimates from the non-pregnant PK studies. In addition, we assumed similar variability in PK

parameters between pregnant versus non-pregnant patients and used the typical parameter estimates for predictions. High variability and bias in these estimates could potentially result in inadequate predictions of the pregnant PK. It should be noted, however, that when relevant changes in these parameters are described, they can be implemented in this model similarly to the other implemented changes. In this respect, the semi-physiological enriched model developed here incorporates similar processes as full physiologically based pharmacokinetic models.

5 Conclusions

The semi-physiological enriched model provided an adequate prediction of the PK for four cytotoxic agents of two distinct drug classes in women over varying stages of gestation. It can be concluded that this proof of principle for a semi-physiological enriched model is applicable to the four cytotoxic drugs in our manuscript and can be extended to drugs with different pharmacological characteristics by the addition of relevant metabolic properties. This method may therefore be used for extrapolation purposes to adjust dosing regimens in pregnant women for drugs for which PK data from pregnant women are unavailable.

Declarations

Author Contributions JMJ, JGCH, DD, FA, KC, JHB, ADRH and TPCD wrote the manuscript; TPCD and ADRH designed the research; JMJ and DD performed the research; JMJ analysed the data.

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Conflict of interest Frédéric C.H. Amant is a senior clinical investigator for the Research Fund-Flanders. All other authors declared no competing interests for this work.

Ethics approval The data used in this study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by institutional review boards and independent ethics committees at participating 137 institutions.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication All individual participants signed informed consent regarding publishing their data.

Availability of Data and Material Not applicable.

Code availability Not applicable.

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