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A simple quantitative model for the prediction of exposure of renally excreted drugs in pregnant women: a comparison with whole body PBPK model

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Abstract

Aim: The objective of this study was to develop a simple quantitative model (SQM) to predict maximum plasma concentration (C_{max}) and the area under the curve (AUC) of renally excreted drugs (n = 16) in pregnant women from non-pregnant women.

Methods: The SQM was developed using 6 physiological parameters and the fraction unbound protein in plasma (f_{up}) as the product characteristic. The six physiological parameters used in this study were total body water, blood volume, cardiac output, glomerular filtration rate (GFR), volume of the fetoplacental unit and blood flow of the fetoplacental unit. A factor was derived based on the average values of the physiological parameters and f_{up} for different gestational ages to predict C_{max} and AUC values in pregnant women from non-pregnant women. The predicted values from SQM were then compared with the dedicated clinical studies as well as predicted values by a physiologically-based pharmacokinetic (PBPK) model.

Results: Out of 17 C_{max} data points, 15 (88.2%), 15 (88.2%), and 12 (70.6%) data points were within 0.5–2.0-fold, 0.5–1.5-fold and 0.7–1.30-fold prediction error, respectively, by SQM, whereas, 17 (100%), 15 (88.2%), and 13 (76.5%) data points were within 0.5–2.0-fold, 0.5–1.5-fold and 0.7–1.30 fold prediction error, respectively, by PBPK. Out of 36 AUC data points, 36 (100%), 34 (94.4%), and 30 (83.3%) data points were within 0.5–2.0-fold, 0.5–1.5-fold and 0.7–1.30-fold prediction error, respectively, by SQM, whereas, 35 (97.2%), 33 (91.7%), and 27 (75%) data points were within 0.5–2.0-fold, 0.5–1.5-fold and 0.7–1.30-fold prediction error, respectively, by PBPK. The results of the study indicated that the predictive power of both models was very good.

Conclusions: The results of the study indicate that the SQM in its predictive performance is as robust and accurate as whole body PBPK.

Keywords

Pregnancy, simple quantitative model, whole body PBPK, C_{max} and AUC, renally excreted drugs

Introduction

Several factors can alter the pharmacokinetics (PK) of a drug needing dose adjustment in a given patient population. These factors are generally known as 'intrinsic' and 'extrinsic' [1]. The examples of intrinsic factors are age, gender, genetics, pregnancy, and disease states such as hepatic and renal impairment [1]. The examples of extrinsic factors are concomitant medicine, smoking, food or beverages (alcohol), malnutrition, water deprivation, and environment [1]. In order to design a safe and effective dose of a medicine in a patient or in a patient population, it is important that both intrinsic and extrinsic factors be taken into account.

Pregnancy leads to substantial anatomical and physiological changes. These changes are important so that the developing fetus can be nurtured for its survival [2]. From the very beginning of conception, these changes begin and affect almost every organ of the body [1, 2].

Significant changes in bodyweight, total body water, blood volume, cardiovascular, glomerular filtration rate (GFR), renal blood flow, and metabolism of a drug can be affected by pregnancy [1, 2]. Total blood volume increases proportionally with cardiac output. The circulating blood volume in pregnancy increases by an average of 45% [3]. An increase in blood volume may lead to decreased concentrations, which may produce the sub-therapeutic effect [4]. Cardiovascular changes start occurring from the early stages of pregnancy. Cardiac output increases by 40% during pregnancy [2, 4]. Pregnancy leads to increased kidney size and weight due to the increased blood volume and vasculature [5, 6]. There is an increase in GFR associated with an increase in creatinine clearance by 30–50% [6]. In short, there are substantial physiological and anatomical changes in pregnancy and these changes may have an impact on the PK characteristics of a drug when administered to pregnant women.

In modern-day drug development, modeling can be helpful in predicting PK parameters and finding suitable dose(s) for ultimate clinical trials in a patient population. Whole body physiologically based-PK (PBPK) models have been suggested [7–9] for the prediction of PK parameters in pregnant women. However, there are examples in the literature that suggest that the whole body PBPK model can be simplified [10–15] to predict PK parameters and dose. Xia et al. [16] suggested a reduced PBPK model to predict AUC of renally excreted drugs in pregnant women (third trimester). Besides using several physicochemical properties and disposition parameters in their model, the authors also used 7 pregnancy-related physiological parameters, and these parameters were body weight, blood volume, cardiac output, volume and blood flow of the fetoplacental unit, volume of total body fat, and GFR.

The objective of this study was to propose a simple quantitative model (SQM) to predict maximum plasma concentration (C_{max}) and area under the curve (AUC) in pregnant women from non-pregnant women for renally excreted drugs using 6 physiological parameters and unbound protein concentration in plasma as a product characteristic (Table 1). The predicted C_{max} or AUC values by SQM were compared with the observed C_{max} or AUC (obtained from dedicated clinical trials) and also with the predicted C_{max} or AUC values from the PBPK model to compare the predictive performance of these two models.

Materials and methods

In this study, the SQM was developed using 6 physiological parameters and unbound protein concentration in plasma as the product characteristic (Table 1). The six physiological parameters used in this study were total body water, blood volume, cardiac output, GFR, volume of the fetoplacental unit and blood flow of the fetoplacental unit. These 6 physiological parameters were chosen due to the substantial impact of pregnancy on them. The gestational age was set up as 12, 24, 30, and 36 weeks [16]. The physiological parameter values in Table 1 are presented as fold change in physiological parameters in pregnant women as compared with non-pregnant women and as a function of gestational age [16]. A factor was developed by

Table 1. Fold change in physiological parameters in pregnant women (compared with non-pregnant women) as a function of gestational age

Parameters (fold change)	GA 12	GA 24	GA 30	GA 36
V fetoplacental unit*	5.60	25.67	43.57	63.43
BF fetoplacental unit*	8.02	20.10	25.21	28.17
Ratio (V/BF)	0.70	1.28	2.19	2.25
Blood volume*	1.08	1.29	1.38	1.43
GFR**	1.22	1.41	1.51	1.60
Total body water**	1.12	1.26	1.32	1.39
Cardiac output**	1.17	1.33	1.40	1.48
Sum	5.29	6.57	7.8	8.15
Average	1.06	1.31	1.56	1.63

* Parameter data from [16]. V fetoplacental unit: volume of fetoplacental unit. BF fetoplacental unit: blood flow of fetoplacental unit. Ratio: volume of fetoplacental unit/blood flow of fetoplacental unit. ** Parameter data from [7]. **Average** consists of Ratio (V/BF), total body water, blood volume, cardiac output, and GFR. The final average for the prediction of C_{max} and AUC for a gestational age (GA) was with the fraction unbound protein.

The following linear equations were developed to predict the following physiological parameters as a function of gestational age [7]. This was done because the reported physiological parameters [7] did not match with the gestational age used in this study (GA 12, 24, 30, and 36 weeks).

$$\text{Total body water} = 0.35 \times \text{GA} + 31.4 \left(r^2 = 0.992\right)$$

$$\text{Cardiac output} = 3.8 \times \text{GA} + 308 \left(r^2 = 0.982\right)$$

$$\text{GFR} = 1.8 \times \text{GA} + 118 \left(r^2 = 0.901\right)$$

Example

An example of calculation of AUC in pregnant women for digoxin is presented. In order to predict C_{max} or AUC for a drug, the fraction unbound protein in plasma will be used as a product characteristic. The fraction unbound protein for digoxin is 0.75. The average for digoxin at GA at week 36 will be 1.48 (average of five ratios in Table 1 plus 0.75 = 1.48). The AUC of digoxin in non-pregnant women was 9.7 ng·hr/mL and in pregnant women in the third trimester or GA 36 weeks, the predicted AUC of digoxin was 9.3/1.48 = 6.3 ng·hr/mL. The observed AUC in pregnant women was 7.3 ng·hr/mL

taking average of the physiological parameter values (fold change from non-pregnant women to pregnant women) along with the fraction unbound protein in plasma for four gestational ages. This factor for the given gestational weeks was then used to predict C_{max} and AUC as shown in Equation 1. An example for the calculation of AUC of a drug in pregnant women is shown in the footnote of Table 1.

$$\text{Predicted } C_{\max} \text{ or AUC in pregnant women} = \frac{\text{Observed } C_{\max} \text{ or AUC in non} - \text{pregnant women or healthy volunteers}}{\text{Factor}} \quad (1)$$

The predicted C_{max} or AUC values by SQM were compared with the observed C_{max} or AUC (obtained from dedicated clinical trials) and also with the predicted C_{max} or AUC values from the PBPK model to compare the predictive performance of these two models.

Sixteen renally excreted drugs were used in this study to predict C_{max} and AUC in pregnant women from Equation 1 in order to validate the predictive performance of the proposed model. The data for these 16 drugs were obtained from the literature [16–23] which had 17 C_{max} and 36 AUC values from dedicated clinical trials. In this study, the whole body PBPK models were not developed; rather C_{max} and AUC values were taken directly from the published PBPK studies [16–23] for comparison purposes with the SQM. The names of drugs (n = 16) used in this study are described below.

Metformin, digoxin, and emtricitabine [16]; ceftazidime, cefuroxime, ceftriaxone, aztreonam, imipenem, and fluconazole [17]; acyclovir, emtricitabine, lamivudine, and metformin [18]; cefazolin, cefuroxime, and cefradine [19]; oseltamivir [20, 21]; amoxicillin [20]; tenofovir [22, 23].

For drugs used in this study, a comparison was also made by taking the ratios of the observed C_{max} and AUC in pregnant women to the observed C_{max} and AUC in non-pregnant women. This comparison provided the magnitude of the difference in the exposure parameters between the non-pregnant and pregnant women.

Statistical analysis

Prediction fold-errors of 2 (0.5–2), 0.5–1.5 (a 50% prediction error on either side of 1) and a more stringent criteria in terms of 0.7–1.3 (a 30% prediction error on either side of 1) were used for the assessment of the

Table 2. A Summary of the number of observations falling within different prediction fold error

Parameters, *n*	Range of prediction fold error	Model			
		SQM	PBPK	SQM, %	PBPK, %
C_{max}, *n* = 17	0.5–2.0	15	17	88.2	100.0
	0.5–1.5	15	15	88.2	88.2
	0.7–1.3	12	13	70.6	76.5
	> 2	2	0	11.8	0.0
AUC, *n* = 35	0.5–2.0	36	35	100.0	97.1
	0.5–1.5	34	33	94.3	91.4
	0.7–1.3	30	27	82.9	74.3
	> 2	0	1	0.0	2.9

SQM: simple quantitative model

predictive performance of the proposed SQM. Considering a very high variability in the PK parameters in pregnant women, a 30–50% prediction error may be considered accurate and acceptable from a clinical perspective [24, 25]. The prediction fold error was calculated as follows:

$$\text{Prediction fold error} = \frac{\text{Predicted PK parameter}}{\text{Observed PK parameter}} \quad (2)$$

Results

In this study, there were 16 drugs with 53 data points (36 for AUC and 17 for C_{max}). The results of this study are summarized below and in Table 2. In Table 3, the C_{max} and AUC values in non-pregnant women/healthy volunteers along with dose, and fraction unbound protein, are provided. In Table 4, the observed (from dedicated clinical trials) and predicted C_{max} and AUC values by SQM and by whole body PBPK (obtained from the literature) are shown. In Tables 5 and 6, the C_{max} and AUC ratios of the studied drugs between pregnant and non-pregnant women are shown. Figures 1 and 2 show a comparison (number of data points versus fold-error) between SQM and PBPK.

Out of 17 C_{max} data points, there were 2 data points whose predicted values by SQM were > 2-fold prediction error. All data points by PBPK model were within 0.5–2-fold prediction error. There were 15 data points (88.2%) that were within 0.5–1.5-fold prediction error by both models, whereas 13 (76.5%) and 12 (70.6%) data points were within 0.7–1.3-fold prediction error by PBPK and SQM, respectively (Table 2).

Out of 36 AUC data points, 36 (100%) and 34 (94.4%), and 30 (83.3%) data points were within 0.5–2.0-fold, 0.5–1.5-fold and 0.7–1.30 fold prediction error, respectively, by SQM, whereas, 35 (97.2%), 33 (91.7%), and 27 (75%) data points were within 0.5–2.0-fold, 0.5–1.5-fold and 0.7–1.30 fold prediction error, respectively, by PBPK (Table 2). The results of the study indicated that the SQM in its predictive performance was as robust and accurate as the whole body PBPK model (Table 2). Overall, predicted C_{max} and AUC values in pregnant women reconciled very well with the observed values by both models.

The comparison of C_{max} and AUC values between pregnant and non-pregnant women indicated that both exposure parameters were lower in pregnant than non-pregnant women. The AUC and C_{max} ratios between pregnant and non-pregnant women ranged from 0.39 to 1.20 (Table 5) and 0.39 to 1.0 (Table 6), respectively. The C_{max} ratio between pregnant and non-pregnant women was > 0.6 for 69% of women and > 0.7 for 62% of women. The AUC ratio between pregnant and non-pregnant women was > 0.6 in 88% of women and > 0.7 in 62% of women. The ratios indicate that despite substantial changes in many physiological parameters in pregnant women than non-pregnant women, there is not much impact of pregnancy on the C_{max} and AUC values for drugs that are renally excreted.

Discussion

PBPK models are used for potential application in clinical pharmacology studies to determine PK or dose for special populations such as pediatrics, pregnancy, and renal and hepatic impairment. Over the years, comparative studies between whole-body and minimal or reduced PBPK models have shown that reduced

Table 3. C_{max} and AUC values used from non-pregnant women/healthy volunteers to predict C_{max} and AUC values in pregnant women

Drugs	Dose (mg), non-pregnant	Unbound protein	Non-pregnant		Ref.
			AUC, mg·hr/L	C_{max}, mg/L	
Metformin	500 mg oral	0.99	9,804**	1,611*	[16, 26]
Digoxin	0.25 mg oral	0.75	9.3**	1.1*	[16, 26]
Emtricitabine	200 mg oral	0.96	9.7**	1.4*	[16, 26]
Ceftazidime	1,000 mg IV	0.85	150	NA	[17]
Ceftazidime	1,000 mg IV	0.85	150	NA	[17]
Cefuroxime	750 mg IV	0.67	82	NA	[17]
Aztreonam	1,000 mg IV	0.44	166	NA	[17]
Ceftriaxone	2,000 mg IV	0.075	1,565	NA	[17]
Imipenem	500 mg IV	0.80	33	NA	[17]
Imipenem	500 mg IV	0.80	33	NA	[17]
Fluconazole	200 mg oral	0.89	175	NA	[17]
Acyclovir	400 mg oral QD	0.79****	3.9	0.80	[18, 26]
Emtricitabine	200 mg QDss oral	0.96	9.8	NA	From Vilade et al. in [18] and [26]
Emtricitabine	200 mg QDss oral	0.96	9.8	NA	From Vilade et al. in [18] and [26]
Emtricitabine	200 mg QDss oral	0.96	9.8	NA	From Vilade et al. in [18] and [25]
Emtricitabine	200 mg QDss oral	0.96	13	2	[18, 23, 26]
Emtricitabine	200 mg QDss oral	0.96	9.7	1.4	From Stek et al. in [18] and [26]
Lamivudine	300 mg QDss oral	0.65	12.7	NA	From Benaboud et al. in [18] and [26]
Metformin	500 mg BID	0.99	9.8	1.6	From Eyal et al. in [18] and [26]
Metformin	500 mg BID	0.99	9.8	1.6	From Eyal et al. in [18] and [26]
Metformin	500 mg BID	0.99	9.8	1.6	From Eyal et al. in [18] and [26]
Metformin	500 mg BID	0.99	9.8	NA	From Liao et al. in [18] and [26]
Metformin	1,000 mg BID	0.99	9.9	NA	From Liao et al. in [18] and [26]
Cefazolin	500 mg IV	0.11	110	NA	[19]
Cefuroxime	750 mg IV	0.67	68	NA	[19]
Cefuroxime	750 mg IV	0.67	68	NA	[19]
Cefradine	500 mg IV	0.80	38.9	NA	[19]
Cefradine	500 mg oral	0.80	31.9	11.8	[19]
OC	75 mg oral	0.97	3,507**	397*	[20, 21]
OC	75 mg oral	0.97	3,507**	397*	[20, 21]
OC	75 mg oral	0.97	3,507**	397*	[20, 21]
Amoxicillin	500 mg oral	0.80	20.4***	NA	[20]
Amoxicillin	500 mg oral	0.80	20.4***	NA	[20]
Tenofovir	300 mg oral	0.93	3.2	0.33	[22, 23, 26]

* C_{max}: ng/mL. ** AUC: ng·hr/mL. *** AUC: μg·hr/mL. **** A middle value between 0.09–0.33. BID: twice daily; f_{up}: fraction unbound protein in plasma; OC: oseltamivir carboxylate; QD: once daily; ss: steady state

Table 4. Predicted and observed C_{max} and AUC by SQM and whole body PBPK

Parameters	Observed	Predicted		Ratios	
	Pregnancy	SQM	PBPK	SQM	PBPK
Metformin (3rd trimester) [16]					
C_{max} (ng/mL)	1,135	1,060	1,068	0.93	0.94
AUC (ng·hr/mL)	6,937	6,450	6,563	0.93	0.95
Digoxin (3rd trimester) [16]					
C_{max} (ng/mL)	0.8	0.7	0.84	0.88	1.05
AUC (ng·hr/mL)	7.3	6.3	8.0	0.86	1.10
Emtricitabine (3rd trimester) [16]					
C_{max} (ng/mL)	1.4	0.9	0.94	0.66	0.67
AUC (ng·hr/mL)	8.0	6.4	8.0	0.80	1.0

Table 4. Predicted and observed C_{max} and AUC by SQM and whole body PBPK (*continued*)

Parameters	Observed	Predicted		Ratios	
	Pregnancy	SQM	PBPK	SQM	PBPK
Ceftazidime; 26.3–33.6 and 37–42 weeks for Caucasian and Japanese, respectively (only AUC values in mg·hr/L [17])					
Caucasian	110	143	95	0.86	1.30
Japanese	120	143	104	0.87	1.19
Cefuroxime; 29 weeks (only AUC values in mg·hr/L [17])					
Caucasian	42	58	40	1.38	0.95
Aztreonam; 25–30 weeks, from Chinese healthy (only AUC values in mg·hr/L [17])					
Japanese	97	121	128	1.25	1.32
Japanese	118	121	142	1.03	1.20
Ceftriaxone; 29 weeks (only AUC values in mg·hr/L [17])					
Caucasian	1,588	1,195	1,868	0.75	1.18
Imipenem; 30-32 weeks, from Chinese healthy (only AUC values in mg·hr/L [17])					
Japanese	27	22	32	0.82	1.19
Japanese	13	22	32	1.70	2.46
Fluconazole; 7.5 weeks (5–10), Chinese healthy (only AUC values in mg·hr/L [17])					
Chinese	121	170	130	1.40	1.07
Acyclovir C_{max} (mg/L); 36 weeks for the first dose (1st) and 38 weeks for the rest [18]					
400 mg PO, first dose	0.70	0.56	0.62	0.80	0.89
400 mg PO TIDss	0.90	0.56	0.72	0.62	0.80
400 mg PO TIDss	0.74	0.56	0.70	0.76	0.95
200 mg PO TIDss	0.43	0.37	0.34	0.86	0.79
Acyclovir, AUC (mg·hr/L) [18]					
400 mg PO, first dose	2.6	2.9	3.7	1.13	1.42
400 mg PO TIDss	3.7	2.9	3.7	0.79	1.00
Emtricitabine [18]					
Valade et al.; AUC (mg·hr/L), dose = 200 mg QD					
15–28 weeks	8.4	7.8	7.5	0.93	0.89
28–40 weeks	8.2	6.7	7.4	0.82	0.90
39 weeks	8.3	6.7	7.7	0.81	0.93
Colbers et al.; dose = 200 mg QD, 28–38 weeks					
C_{max} (mg/L)	1.8	1.4	1.5	0.76	0.83
AUC (mg·hr/L)	9.6	8.9	7.6	0.93	0.79
Stek et al.; 31–38 weeks					
C_{max} (mg/L)	1.4	1.0	1.5	0.78	1.07
AUC (mg·hr/L)	8.0	6.6	7.5	0.85	0.94
Lamivudine; dose = 300 mg PO steady state, 36–40 weeks					
AUC (mg·hr/L)	12.5	9.1	10.5	0.73	0.84
Metformin [18]					
Eyal et al.; dose = 500 mg PO BID, C_{max} (mg/L)					
10–14 weeks	1.22	1.45	1.27	1.19	1.04
22–26 weeks	1.06	1.28	1.20	1.21	1.13
34–38 weeks	1.14	1.10	1.23	0.96	1.08
Eyal et al.; dose = 500 mg PO BID, AUC (mg·hr/L)					
10–14 weeks	6.5	9.3	8.2	1.37	1.26
22–26 weeks	6.1	7.8	7.7	1.29	1.26
34–38 weeks	6.9	6.7	8.1	0.97	1.17
Liao et al.; dose = 500 mg PO BID; 26–38 weeks					
AUC (mg·hr/L)	7.7	6.7	7.9	0.88	1.03
Liao et al.; dose = 1,000 mg PO BID; 26–38 weeks					
AUC (mg·hr/L)	11.9	6.7	16.5	0.57	1.39

Table 4. Predicted and observed C_{max} and AUC by SQM and whole body PBPK (*continued*)

Parameters	Observed	Predicted		Ratios	
	Pregnancy	SQM	PBPK	SQM	PBPK
Cefazolin; 500 mg IV, 19–33 weeks [19]					
AUC (mg·hr/mL)	76	83	67	1.10	0.89
Cefuroxime; 750 mg IV, AUC (mg·hr/mL) [19]					
13 weeks (11–35 week)	42	48	43	1.15	1.02
42 weeks	47	46	46	0.99	0.99
Cefradine; 500 mg IV, AUC (mg·hr/mL) [19]					
15 weeks (10–29)	24	27	26	1.12	1.05
Cefradine; 500 mg oral, 20 weeks (13–33) [19]					
C_{max} (mg/L)	6.1	7.9	6.2	1.30	1.02
AUC (mg·hr/mL)	25.3	21.4	15.7	0.85	0.62
Oseltamivir Carboxylate, C_{max} (ng/mL) [20, 21]					
First trimester	150	378	297	2.52	1.98
Second trimester	153	318	270	2.08	1.76
Third trimester	198	272	283	1.37	1.43
Oseltamivir Carboxylate, AUC (ng·hr/mL) [20, 21]					
First trimester	1,828	3,340	2,469	1.83	1.35
Second trimester	2,325	2,806	2,226	1.21	0.96
Third trimester	2,367	2,402	2,381	1.01	1.01
Amoxicillin, AUC (µg·hr/mL)					
Second trimester	15.2	16.6	24.4	1.07	1.61
Third trimester	14.9	14.0	24.0	0.94	1.61
Tenofovir, third trimester [22]					
C_{max} (mg/L)	0.28	0.23	0.27	0.81	0.96
AUC (mg·hr/L)	2.5	2.3	1.7	0.91	0.68

SQM: simple quantitative model; ss: steady state; TID: three times daily

PBPK models are as robust and accurate as whole-body PBPK models [10–15]. A reduced PBPK model uses only a few physiological parameters (as few as 4–5) and is much simpler to develop than a whole-body PBPK model. The comparable prediction accuracy of reduced PBPK models with whole-body PBPK models raises scientific and practical questions about whether the extent of physiological parameters used in a whole-body PBPK model is necessary.

In this study, six physiological parameters and only one parameter in terms of drug characteristic, namely fraction unbound protein in plasma, were used. The objectives of the study were to design an SQM to predict C_{max} and AUC of renally excreted drugs for pregnant women without the need for specialized software and extensive data analysis. Pregnancy impacts all physiological parameters [5], and logically, one will consider including all the affected physiological parameters in a model. However, the experience with reduced PBPK models indicates that it is not necessary to use all physiological parameters in a PBPK model rather the model can be substantially simplified [13, 16]. Xia et al. [16] used a minimal physiological model to predict the exposure of 3 renally excreted drugs and one hepatically metabolized drug in the third trimester.

The current study, like previous studies [10–15] clearly indicates that one does not need 10–12 physiological parameters as well as several drug related physico-chemical properties to predict drug exposure in pregnant women. These observations also indicate that the accuracy of the models to achieve the intended objective does not improve by adding complexity or unnecessary parameters (i.e., reduced vs whole body PBPK).

A comparison of the C_{max} and AUC values in pregnant women with non-pregnant women indicates that in pregnancy, drug exposure for renally excreted drugs may not be reduced substantially. For the drugs used in this study, the C_{max} and AUC ratio between pregnant and non-pregnant women ranged from 0.39 to

Table 5. AUC values and ratio between non-pregnant/healthy volunteers and pregnant women [16–23, 26]

Drugs	Pregnancy	Non-pregnant, mg·hr/L	Pregnant, mg·hr/L	Ratio, preg/non-preg
Metformin	3rd trimester	9,804*	6,937	0.71
Metformin	10–14 weeks	9.8	6.5	0.66
Metformin	22–26 weeks	9.8	6.1	0.62
Metformin	34–38 weeks	9.8	6.9	0.70
Metformin	26–38 weeks	9.8	7.7	0.79
Metformin	26–38 weeks	9.9	11.9	1.20
Digoxin	3rd trimester	9.3*	7.3*	0.78
Emtricitabine	3rd trimester	9.7**	8.0**	0.82
Emtricitabine	15–28 weeks	9.8	8.4	0.86
Emtricitabine	28–40 weeks	9.8	8.2	0.84
Emtricitabine	39 weeks	9.8	8.3	0.85
Emtricitabine	28–38 weeks	13.0	9.6	0.74
Emtricitabine	31–38 weeks	9.7	8.0	0.82
Lamivudine	36–40 weeks	12.7	12.5	0.98
Ceftazidime	29 weeks	150	110	0.73
Ceftazidime	39 weeks	150	120	0.80
Cefuroxime	30–37 weeks	82	42	0.51
Aztreonam	25–30 weeks	166	97	0.58
Aztreonam	25–30 weeks	166	118	0.71
Ceftriaxone	29 weeks	1,565	1,588	1.01
Imipenem	40 weeks	33	27	0.82
Imipenem	40 weeks	33	13	0.39
Fluconazole	30–37 weeks	175	121	0.69
Cefazolin	19–33 weeks	110	76	0.69
Cefuroxime	11–35 weeks	68	42	0.62
Cefuroxime	42 weeks	68	47	0.69
Cefradine (IV)	10–29 weeks	39	24	0.62
Cefradine (oral)	13–33 weeks	32	25	0.78
Oseltamivir	First trimester	3,507*	1,828*	0.52
Oseltamivir	Second trimester	3,507*	2,325*	0.66
Oseltamivir	Third trimester	3,507*	2,367*	0.67
Amoxicillin	Second trimester	20**	15.2**	0.76
Amoxicillin	Third trimester	20**	14.9**	0.75
Tenofovir	Third trimester	3.2	2.5	0.78

* ng·hr/mL. ** µg·hr/mL

1.0 and 0.39 to 1.20, respectively. It can be seen from this study that the change in the magnitude of exposure is highly variable. For many drugs, pregnancy has a negligible impact on the exposure of renally excreted drugs.

Lower exposure of a drug in pregnancy will require dose adjustment in pregnant women and can widely vary. One can also observe different exposure values for the same drugs in different studies. For example, two studies on imipenem in Japanese pregnant women provided two different results [17]. One study indicated that the AUC of imipenem in pregnant women was 82% of that in non-pregnant women and the other study indicated that the AUC of imipenem in pregnant women was 39% of that in non-pregnant women (Table 5).

In pregnancy, the dose adjustment will require a correct estimate of the change in the magnitude of exposure of a given drug. A 2-fold prediction error or even a 50% prediction error from a model may not be acceptable for the selection of the 'right dose' in pregnant women. Inaccurate dosing will lead to harmful effects to both the mother and the fetus; hence, a dedicated clinical trial is needed.

Table 6. C_{max} values and ratio between non-pregnant/healthy volunteers and pregnant women [16–23, 26]

Drugs	Pregnancy	Non-pregnant, mg/L	Pregnant, mg/L	Ratio, preg/non-pregnant
Metformin	3rd trimester	1.6	1.14	0.71
Metformin	10–14 weeks	1.6	1.22	0.76
Metformin	22–26 weeks	1.6	1.06	0.66
Metformin	34–38 weeks	1.6	1.14	0.71
Digoxin	3rd trimester	1.1*	0.8*	0.73
Emtricitabine	3rd trimester	1.4**	1.4**	1.00
Emtricitabine	28–38 weeks	2.0	1.8	0.90
Emtricitabine	31–38 weeks	1.4	1.4	1.0
Cefradine (oral)	13–33 weeks	11.8	6.1	0.52
Oseltamivir carboxylate	First trimester	397*	150*	0.39
Oseltamivir carboxylate	Second trimester	397*	153*	0.40
Oseltamivir carboxylate	Third trimester	397*	198*	0.52
Tenofovir	38 weeks	0.33	0.28	0.85

* C_{max}: ng/mL. ** μg/mL

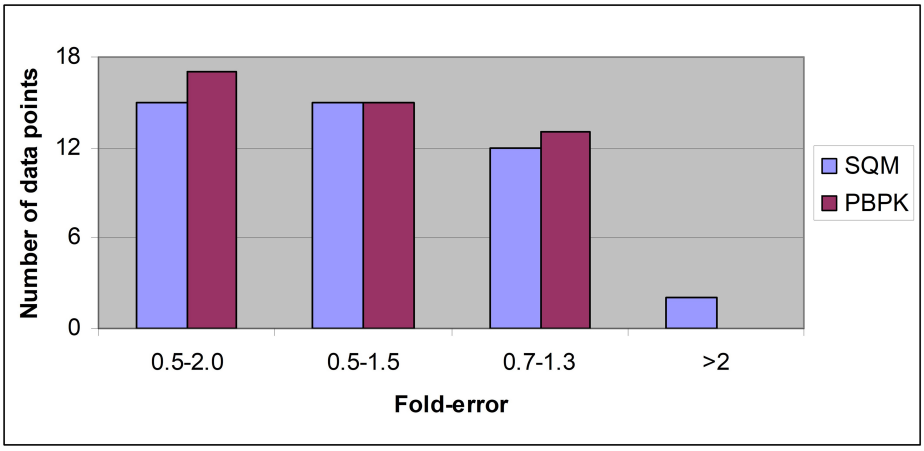

Figure 1. A comparison of C_{max} values (number of data points within fold-error) between SQM and PBPK. SQM: simple quantitative model

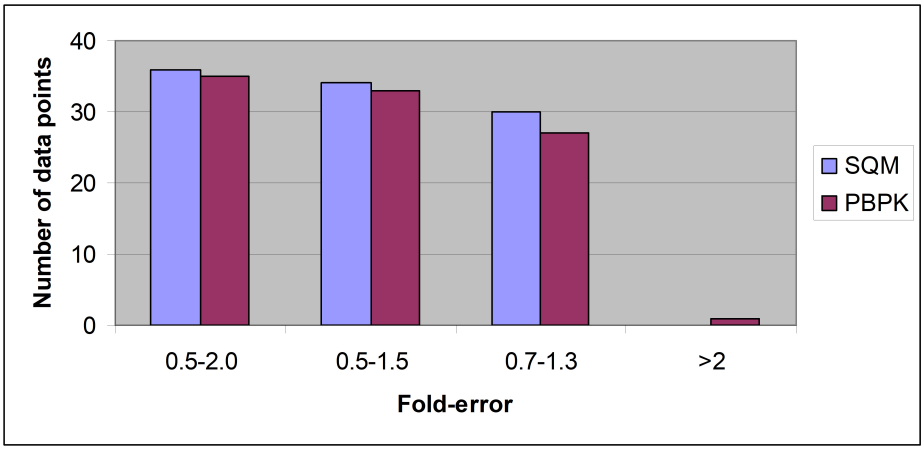

Figure 2. A comparison of AUC values (number of data points within fold-error) between SQM and PBPK. SQM: simple quantitative model

It is well established that all models (allometry, physiological, or pharmacometrics) have uncertainty and some degree of inaccuracy because a model's accuracy is based on the assumptions and information provided to the model. The true biological or physiological mechanisms are barely known; therefore, assumptions are made that may or may not be correct and are generally based on convenience for modeling. In a biological world, models only represent a small fraction of the biological or physiological

events that are known. Modeling in a biological system is far more complex than in a physical system. Nevertheless, modeling is a reasonable approach in early drug development and can provide important practical guidance in drug development. Considering the nature of the models, dedicated clinical trials will be needed in pregnant women for the selection of the 'right dose'.

Simple and pragmatic models, due to the ease of implementation with acceptable predictive performance, are highly desirable and are expected to expedite the development of therapeutic products. This study demonstrates that an SQM using only six physiological parameters and one parameter as a product characteristic can be developed with reasonable accuracy for the prediction of drug exposure in pregnant women. This proposed simple model does not require any specialized software and extensive data analysis rather the entire calculation can be done on an Excel worksheet. The proposed model in pregnancy can support in choosing an appropriate dose in clinical trials to select the right dose to provide therapeutic benefit to pregnant women.

Abbreviations

AUC: area under the curve

C_{max}: maximum plasma concentration

f_{up}: fraction unbound protein in plasma

GFR: glomerular filtration rate

PBPK: physiologically based-pharmacokinetics

PK: pharmacokinetics

SQM: simple quantitative model

Declarations

Author contributions

IM: Conceptualization, Investigation, Writing—review & editing.

Conflicts of interest

The author has no conflict of interest.

Ethical approval

Data were taken from the literature; hence, ethical approval is not required.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

All data supporting the findings of this study are available within the manuscript and its cited references. Further analytical data are available from the corresponding author upon reasonable request.

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