Pharm Res (2012) 29:1609–1617
DOI 10.1007/s11095-012-0671-2

RESEARCH PAPER

Leveraging Physiological Data from Literature into a Pharmacokinetic Model to Support Informative Clinical Study Design in Pregnant Women

J. G. Coen van Hasselt • Bruce Green • Glynn A. Morrish

Received: 14 September 2011 / Accepted: 3 January 2012 / Published online: 13 January 2012

ABSTRACT

Purpose Physiological changes during pregnancy can effect pharmacokinetic (PK) parameters, which may lead to altered dose requirements. We aimed to leverage literature-based physiological changes during pregnancy into a PK model and compare its performance to a published reference model in pregnant women and to use the literature-based model to determine informative PK sampling times for a clinical study that aims to quantify the PK of enoxaparin throughout pregnancy.

Methods Changes in total body water (BW) and creatinine clearance (CRCL) during pregnancy were described using regression models. BW and CRCL were linked to a PK model of enoxaparin in non-pregnant women. Performance of the literature-based PK model was compared to a previously published empirical reference model. D-optimal sampling times were determined and evaluated for literature-based and reference models.

Results The literature-based model adequately predicted anti-Xa plasma concentrations when compared to reference model predictions. An informative sampling design was succesfully developed, with parameters expected with good precision (RSE < 36.4%).

Conclusion A literature-based model describing enoxaparin PK during pregnancy was developed and evaluated. The modelling framework could be used to support development of informative designs in pregnancy when prior models are unavailable.

KEY WORDS enoxaparin · NONMEM · optimal design · pharmacokinetics · pregnancy

ABBREVIATIONS

BW	body water
BW_0	pre-pregnancy body water
BW_{MAX}	maximum change in body water
BW_{50}	half-maximum change in body water
BW_γ	Hill coefficient for body water
CL	clearance
CL_{NP}	non-pregnant clearance
CL_{NR}	non-renal clearance
CL_R	renal clearance
CRCL	creatinine clearance
$CRCL_0$	non-pregnant creatinine clearnace
$CRCL_{MAX}$	maximum change in creatinine clarance
$CRCL_{50}$	half-maximum change in creatinine clearance
f_e	fraction of renal clearance
IU	international units
PD	pharmacodynamics
PK	pharmacokinetics
RSE	relative standard error
RUV	residual unexplained variability
SCR	serum creatinine
V	volume

J. G. C. van Hasselt (✉)
Department of Pharmacy and Pharmacology
Netherlands Cancer Institute/Slotervaart Hospital
Louwesweg 6, PO Box 90440
1006 BK Amsterdam, The Netherlands
e-mail: jgc.vanhasselt@gmail.com

B. Green · G. A. Morrish
Model Answers Pty Ltd.
Brisbane, Australia

G. A. Morrish
Goodness of Fit Pty Ltd.
Brisbane, Australia

J. G. C. van Hasselt
School of Pharmacy, University of Queensland
Brisbane, Australia

B. Green
School of Medicine, University of Queensland – Mater Clinical School
Brisbane, Australia

V_{NP}	non-pregnant volume of distribution
WT	body weight
WT0	pre-pregnancy body weight

INTRODUCTION

Physiological changes during pregnancy can effect pharmacokinetic (1) (PK) parameters and therefore drug disposition. Pregnancy related physiological changes include an alteration in renal function (1,2), changes in the activity of drug metabolizing enzymes (1), changes in cardiac output (1) and expansion of intravascular plasma volume and extravascular water content (3). Therefore, the dosing regimen of drugs administered during pregnancy may need to be altered to optimize therapy, depending upon the magnitude of change in PK, and the drugs therapeutic index.

PK trials that seek to learn about dose requirements during pregnancy are however difficult to perform due to limited PK sampling opportunities, with trials commonly comprising of unscheduled outpatient visits only. Development of informative limited PK sampling designs (using methods such as D-optimality (4) or simulation) to overcome these challenges are further complicated by potential changes in physiology and PK during the gestational period. As such, PK sampling times may need to be varied during the course of the study, to ensure PK parameters can be estimated with good precision across the entire gestational period. Determining if this is warranted requires a prior model over which sampling times are optimized. Unfortunately, few models describing PK during pregnancy have been published (5–7), limiting the use of D-optimality as a design tool for studies in this population.

This manuscript uses enoxaparin as a motivating example to explore if PK sampling would need adaptation during pregnancy, to ensure parameters can be estimated with good precision across the entire gestational period. Enoxaparin is a subcutaneously administered low-molecular weight heparin (LMWH), used for the prevention and treatment of deep vein thrombosis, pulmonary embolism and various other thromboembolic conditions (8,9). Pregnant women are five to six times more likely to have a thromboembolic event compared to non-pregnant women (10), with the incidence further increased in the presence of acquired or congenital thrombophilia, and a past medical history of such events (11–13).

Anti-Xa activity (measured in international units (IU)/ml) is widely used as a marker of enoxaparin concentration (6,14), with enoxaparin PK derived from anti-Xa activity. Minimum therapeutic anti-Xa levels have been reported between 100 and 200 IU/L (15). This narrow therapeutic index, combined with the significant clinical consequences of under or overdosing, highlights the importance of characterizing the PK of enoxaparin during pregnancy.

As enoxaparin is hydrophilic and primarily eliminated via the kidneys (16), physiological changes in pregnancy are likely to have an impact on clearance (CL) and volume of distribution (V), which has been supported in small observational studies (17–19).

The objectives of this work were to a) develop a literature-based PK model for enoxaparin during pregnancy from existing literature and compare its performance to a published reference model and b) use the literature-based model to determine informative PK sampling times for a clinical study that aims to quantify the PK of enoxaparin throughout pregnancy.

METHODS

Development and Evaluation of the Literature-Based PK Model

Incorporation of Physiological Variables in the Literature-Based Model

A literature study was conducted to identify publications that reported on changes in physiological variables during pregnancy. Variables considered were: body weight, cardiac output, creatinine clearance, fat free mass, glomerular filtration rate, plasma volume, and total body water. Relevant physiological variables were selected based on the availability of data across different terms of pregnancy, and their expected relevance to enoxaparin PK. The most relevant physiological values were included in a PK model by the rational described in the following section.

Given that enoxaparin is hydrophilic, remains largely within the intravascular space and is renally cleared, total body water (BW) and creatinine clearance (CRCL) were considered the most significant physiological variables likely to influence CL and V, respectively, during pregnancy. Literature data describing changes in BW and CRCL were evaluated and non-linear regression models were developed to describe the mean change in BW and CRCL during pregnancy. For the regression, data points were weighted for the number of subjects in each available study. For BW and CRCL, we aimed to use Emax-type models in order to capture the nonlinear nature of changes in physiological variables.

The regression models describing changes over the pregnancy period in BW (20–23) (BW(t)) and CRCL (6,24) (CRCL(t)) were then linked to published PK parameters

Table I Enoxaparin Population PK Parameter Values for Non-pregnant and Pregnant Women, Obtained from Lebaudy *et al* (6). Depicted Parameter Values Represent Median Values Obtained from a Non-parametric Bootstrap Analysis, Since not all Point Estimates were Reported by this Analysis

Description	Parameter	Estimate
Population parameters non-pregnant women		
Clearance	CL_{NP} (L/h)	0.524
Volume	V_{NP} (L)	7.30
Population parameters pregnant women		
Clearance	CL_{PR} (L/h)	0.81
Volume	V_{PR} (L)	7.81
Absorption rate constant	[a]K_A (h^{-1})	0.56
Pregnancy effect on CL	RATIO (−)	0.42
Pregnancy effect on V	GEST (−)	1.41
Inter-individual variability[a]		
Clearance	CL (CV%)	20.3
Volume	V (CV%)	26.0
Residual variability[a]		
	Additive error (IU/L, SD)	120

IIV Inter-individual variability, *IU* International units, *CV* Coefficient of variation, *SD* Standard deviation

[a] These parameters appeared to be estimated for the pregnant population, but were also used for the model of enoxaparin in non-pregnant women

(Table I) for enoxaparin in non-pregnant females (6). Enoxaparin clearance is a function of renal and non-renal clearance. Therefore, total non-pregnant clearance (CL_{NP}) was divided into renal (CL_R) and non-renal clearance (CL_{NR}) based on the ratio described by Green *et al* (14), who reported a fraction of non-renal clearance (F_{NR}) of 0.25, and a fraction of renal clearance (f_e) of 0.75.

The value of non-pregnant CL_R was corrected for changes in renal function during pregnancy by multiplying with the normalized change in CRCL. CRCL was normalized by the pre-pregnancy value ($CRCL_0$), so that the normalized CRCL reflects the change in renal function during pregnancy.

Enoxaparin is primarily metabolized hepatically by depolymerization and desulfation to lower weight fragments. Although changes in hepatic metabolism are known to occur during pregnancy, these have not been reported for these specific metabolic processes. Therefore, the hepatic elimination of enoxaparin was assumed to remain unchanged over pregnancy.

The non-pregnant value of volume of distribution (V_{NP}) was corrected for changes in BW, by multiplying with BW, normalized by initial body water (BW_0).

Finally, values of CL and V prior to start of pregnancy, were scaled using a ¾-allometric power model (25) using the pre-pregnancy body weight (WT_0), to account for differences in body size between subjects prior to pregnancy. The rationale for allometric scaling CL and V is described by Holford *et al.* (26). The model did not include the actual change in body weight during pregnancy, because the physiological changes relevant to enoxaparin were captured by the change in CRCL and BW. The resulting PK parameters for the literature-based model are depicted in Eqs. 1–3.

$$CL_R(t) = CL_{NP} \cdot f_e \cdot \left(\frac{WT_0}{median(WT_0)}\right)^{3/4} \cdot \left(\frac{CRCL(t)}{CRCL_0}\right) \quad (1)$$

$$CL_{NR} = CL_{NP} \cdot F_{NR} \cdot \left(\frac{WT_0}{median(WT_0)}\right)^{3/4} \quad (2)$$

$$V(t) = V_{NP} \cdot \left(\frac{WT_0}{median(WT_0)}\right) \cdot \left(\frac{BW(t)}{BW_0}\right) \quad (3)$$

Since population parameter estimates for K_A, inter-individual variability (IIV) on CL and V, and residual unexplained variability (RUV) were only reported for pregnant women (6), these parameters were assumed to remain unchanged in non-pregnant women.

Reference Model

The performance of the literature-based model was compared to a published model that described pregnancy-varying PK of enoxaparin (6), herein referred to as the 'reference model'. The reference model had one compartment disposition with first-order absorption and elimination. The change in CL over pregnancy (Eq. 4) was described using the covariates WT and serum creatinine (SCR), and an empirical covariate effect parameter *RATIO*.

$$CL_{REF}(t) = CL_{PR} \cdot \left(\frac{WT(t)/SCR(t)}{1.27}\right)^{RATIO} \quad (4)$$

The change in V (Eq. 5) was described using WT and the parameter GEST:

$$V_{REF}(t) = V_{PR} \cdot \left(\frac{WT(t)}{70}\right) \cdot GEST \quad (5)$$

In this equation, *GEST* equals 1 if gestational weeks <31, and *GEST* equals 1.41 if gestational weeks ≥31. All parameters used in the reference model are given in Table I. The authors of the reference model did not report all parameter point estimates for this model, however they did report all median bootstrap estimates. Therefore we chose to use the median bootstrap parameter estimates in this analysis. The difference

between key parameters such as clearance is only marginal (e.g. 0.81 point estimate *versus* 0.781 bootstrap estimate).

In order to obtain predictions for the reference model across pregnancy to allow for comparison between models, empirical polynomial based regression models were also developed for the physiological variables SCR and WT, based on literature values. The mean change in SCR was modeled according to the values reported over pregnancy by Lebaudy *et al* (6), and WT was modeled based on a study reported by Ochsenbein-Kolbe (27).

Evaluation of the Literature-Based Model Predictions

In order to compare predictions between the literature-based and reference models, 1,000 individual concentration-time profiles were simulated stochastically using both models. Simulations were conducted for a prophylactic treatment, with a dose of 4,000 IU daily. Dense sampling times (9 samples after each dose) were used so that simulated peak and trough levels for enoxaparin could be accurately determined. For these simulations, the estimated regression models of the physiological variables for the literature-based model (CRCL, BW) and the reference model (SCR, WT) were used. Estimates for inter-individual and residual variability were used as reported by Lebaudy *et al* (6). Subsequently, median and 80% prediction intervals for the anti-Xa peak and trough values *versus* time were calculated and overlaid graphically (Fig. 3).

Furthermore, anti-Xa peak mean values as observed in the study by by Casele *et al* (19) investigating enoxaparin PK during pregnancy have been included in Fig. 3

Determination of Informative Enoxaparin PK Sampling Times

Optimal Sampling Times

Sampling windows were calculated for the literature-based and reference models using D-optimality, under the practical constraints defined by the coordinators of the clinical study (Table II). Optimal sampling times were determined for each planned occasion, separately (0, 2, 4, 6, and 8 months), based on the predicted changes in PK parameters for the literature-based and reference models, respectively.

Table II Study Design Details and Constraints for the Evaluated Clinical Study Investigating Enoxaparin PK during Pregnancy

Design aspect	Value
Fixed sample size	72
Fixed dose (IU)	4,000
Fixed sampling occasions (months)	0, 2, 4, 6, 8
Maximum number of samples per occasion	3
Constraints of sampling time	within −0.5 to 3 h post-dose

IU International Units

Evaluation of Sampling Designs

The optimal sampling designs for the literature-based and reference models were evaluated by simulating 1,000 individual concentration-time profiles under the design of interest using the reference model, then re-estimating the PK parameters using the reference model.

For simulation of data, the estimated regression models for SCR and WT were again incorporated. In addition, to obtain a more realistic simulation of the anticipated clinical study, variability was included on covariate values. Inter-individual variability was assumed to be 33 CV% for SCR and 23 CV% for WT, and 9.8 CV% within subject variability (WSV) for SCR and 1.8 CV% WSV for WT, for simulated values for SCR and WT across pregnancy. These values were derived from a repeated measures dataset of approximately 1,000 cancer patients (unpublished data). A correlation of r=0.1 was assumed between IIV in SCR and WT, based on the correlation estimated in an unrelated clinical dataset (28). Any covariate values of SCR and WT below zero were truncated.

The bias and precision of the PK parameter estimates obtained for the literature-based and reference model designs were computed and compared. Bias was calculated using the mean relative error (MRE) between the "true" parameter estimate from the reference model (used to simulate the data), and the estimated parameter value $\hat{y}$, which was computed as depicted in Eq. 6. Precision was computed using the relative standard error (RSE) of the parameter (Eq. 7).

$$MRE = mean\left(\left|\frac{true - \hat{y}}{true}\right|\right) \cdot 100 \quad (6)$$

$$RSE = \frac{sd(\hat{y})}{mean(\hat{y})} \cdot 100\% \quad (7)$$

Software

The regression equations fitted to the physiological variables were developed using R (version 2.9.0) together with the nonlinear least squares (nls) function. Simulations of the two models were performed in NONMEM (version 7.1.0) (29).

D-optimal designs were determined using WinPOPT (version 1.2) using the exchange optimization algorithm (30).

RESULTS

Development and Evaluation of the Literature-Based Model

Incorporation of Physiological Variables in the Semi-physiological Model

The mean change in CRCL and BW during pregnancy were used as input functions for the literature-based model. Therefore, regression models for pooled literature values for CRCL (6,24) and BW (20–23) were developed. The aim of these regression equations was to describe the mean change of these variables during pregnancy. The developed regression equations are described by Eqs. 8 and 9.

$$CRCL(t) = CRCL_0 + \left(\frac{CRCL_{MAX} \times t}{CRCL_{50} + t}\right) \tag{8}$$

$$BW(t) = BW_0 + \left(\frac{BW_{MAX} \times t^{BW\gamma}}{BW_{50}^{BW\gamma} + t^{BW\gamma}}\right) \tag{9}$$

Here, $CRCL_0$ represent baseline CRCL, $CRCL_{MAX}$ represents the maximum change in CRCL, $CRCL_{50}$ represents the time of the half-maximum change in CRCL, BW_0 represents baseline BW, BW_{MAX} represents the maximum change in BW, BW_{50} represents the time of half-maximum change in BW, and BW_γ represents a sigmoidal Hill coefficient. The unit of time in these regression equations is gestational weeks.

Emax and sigmoidal Emax equations were chosen to describe these processes, because of the inherent presence of a maximum in the change of a physiological parameter, and the nonlinear nature of the observed change. Extended Emax equations incorporating the post-partum change were also evaluated, but these were found to be poorly identifiable, given the available data. For CRCL, a sigmoidal Emax relation could not be reliably estimated. No other equations were considered to describe these variables. The estimates and relative standard errors (RSEs) of the regression coefficients are given in Table III.

These regression equations were evaluated based on visual fit (Fig. 1) and parameter estimation precision (Table III). This visual fit for both physiological variables appeared adequate. The precision (RSE, %) of the regression coefficients for CRCL were 3.91, 12.48 and 37.59 for $CRCL_0$, $CRCL_{MAX}$ and $CRCL_{50}$ respectively and were considered acceptable given the limited data available. For BW, the precision (RSE,%) was 2.64, 13.97, 1.26 and 77.55 for BW_0, BW_{MAX}, BW_{50} and BW_γ respectively. We considered all parameter to be estimated with adequate precision. For BW, large variability in literature reported mean values was present across different studies.

Reference Model

Similar to the literature-based model, polynomial regressions equations were fitted to describe literature values for WT (27) and SCR (6), in order to support the reference model. In contrast to Eqs. 8 and 9, for the reference model, fully empirical polynomial equations were considered adequate, as these were only used to support comparison of model predictions. The developed equations are as shown below (Eqs. 10 and 11 with the corresponding parameter estimates reported in Table III.

$$WT(t) = WT_a \cdot t^4 + WT_b \cdot t^3 + WT_c \cdot t^2 + WT_d \cdot t + WT_0 \tag{10}$$

$$SCR(t) = SCR_a \cdot t^3 + SCR_b \cdot t^2 + SCR_c \cdot t + SCR_0 \tag{11}$$

The regression equations were evaluated based on parameter precision and visual fit. The predicted values adequately fitted to the reported literature values (Fig. 2). For WT, the parameter precision was <42% RSE, except for one regression coefficient (RSE 1792%). However, exclusion of this parameter caused a less optimal fit based on visual inspection. Since overall visual fit was good, and the only aim of this regression was to support comparison of predictions, this model was used for further analysis. The time-scale for weight was changed to units of 10 gestational weeks, in order to scale the magnitude of the parameter estimates to numerically stable values. For SCR, parameter precision ranged between 3.0 and 65.4 RSE%, and the time scale was in gestational weeks.

Evaluation of the Literature-Based Model Predictions

Stochastic simulations of anti-Xa peak and trough concentrations using the literature-based and reference models showed comparable concentration-time profiles (Fig. 3). Some overprediction of peak Anti-Xa levels was observed for the literature-based model. This discrepancy seemed to be caused partially by the abrupt change in model parameters which are predicted by the refence model for non-pregnant *versus* pregnant women, and another instanteneous change in V at >31 gestational weeks. Overall, the change in Anti-Xa peak and trough levels troughout pregnancy appeared to show a similar trend.

Table III Regression Coefficients Describing the Change in Total Body Water (BW), Creatinine Clearance (CRCL), Body Weight (WT), and Serum Creatinine (SCR) Throughout Pregnancy. The Associated Regression Equations are Depicted in Eqs. 7–10

Creatinine clearance			Total body water			Body weight			Serum creatinine		
Parameter	Estimate	(RSE)	Parameter	Estimate	(RSE)	Parameter	Estimate	(RSE)	Parameter	Estimate	(RSE)
$CRCL_0$	5.866	(3.91)	BW_0	32.56	(2.64)	WT_a	0.5433	(19.03)	SCR_a	−0.0005747	(65.39)
$CRCL_{MAX}$	5.029	(12.48)	BW_{MAX}	8.304	(13.97)	WT_b	0.0164	(1792)	SCR_b	0.05794	(40.76)
$CRCL_{50}$	13.34	(37.59)	BW_{50}	30.16	(1.26)	WT_c	0.7589	(42.03)	SCR_c	−1.771	(24.76)
			BW_γ	54.03	(77.55)	WT_d	−0.0881	(13.59)	SCR_d	71.75	(3.035)
						WT_0	60.188	(0.19)			

RSE Relative standard error, $CRCL_0$ represent baseline CRCL, $CRCL_{MAX}$ represents the maximum change in CRCL, $CRCL_{50}$ represents the time of the half-maximum change in CRCL, BW_0 represents baseline BW, BW_{MAX} represent s the maximum change in BW, BW_{50} represents the time of half-maximum change in BW, and BW_γ represents a sigmoidal Hill coefficient.

Determination of Informative Enoxaparin PK Sampling Times

Optimal Sampling Times

D-optimal timepoints and sampling windows for the literature-based model and the reference model were found to be comparable (Table IV), except for the second blood sample, which is located in the absorption phase for enoxaparin (literature-based model: 0.58 h *versus* reference model: 1.3 h). The first and third sampling points were located at the boundaries of the predefined clinical study design.

The change in parameter estimates over pregnancy resulted in a neglible change of optimal sampling times for the reference model (0.01 h). No change in sampling times was found for the literature-based model, which is related to decreased magnitude of change in PK parameters compared to the reference model.

Evaluation of Sampling Designs

Re-estimation of reference model parameters with the design based on the literature-based and the reference model showed comparable precision and bias (Table V). For the literature model, precision (RSE) was <16% for fixed effects and <36% for random effects. Bias was below 3.9% for fixed effects and below 7.1% for random effects.

DISCUSSION

Physiological changes that occur during pregnancy should be considered when designing trials that learn about PK. In this manuscript, we demonstrated how literature data was used to construct a literature-based model for enoxaparin, which could predict changes in PK across pregnancy. The predictive performance of this literature-based model was

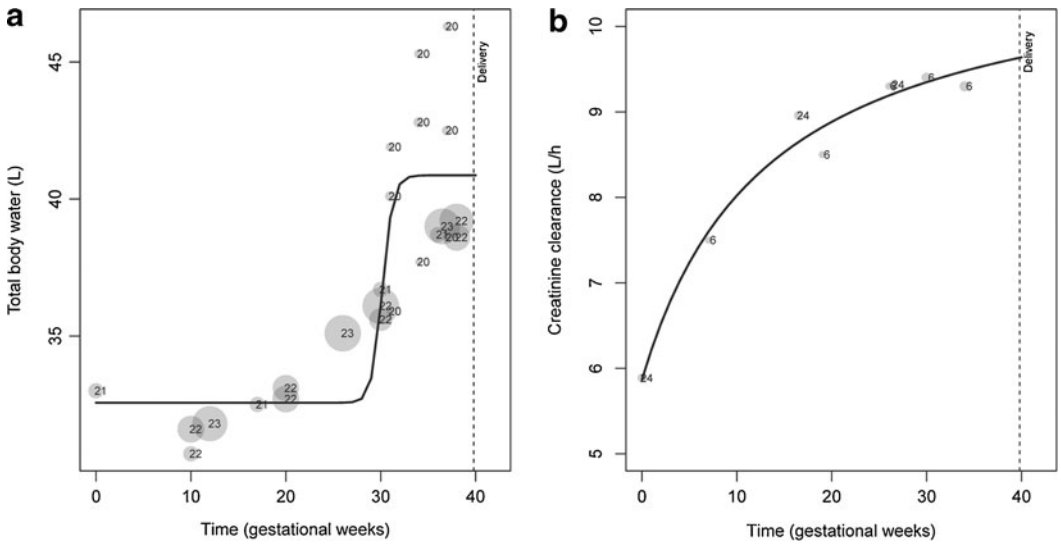

Fig. 1 Mean change in total body water (L) and creatinine clearance (L/h) *versus* time (gestational weeks), based on literature values. The *solid line* represents the model fit. The *circles* represent reported mean data from different studies, with the circle diameter representing the number of samples used in the study. The *numbers* represent references to associated studies.

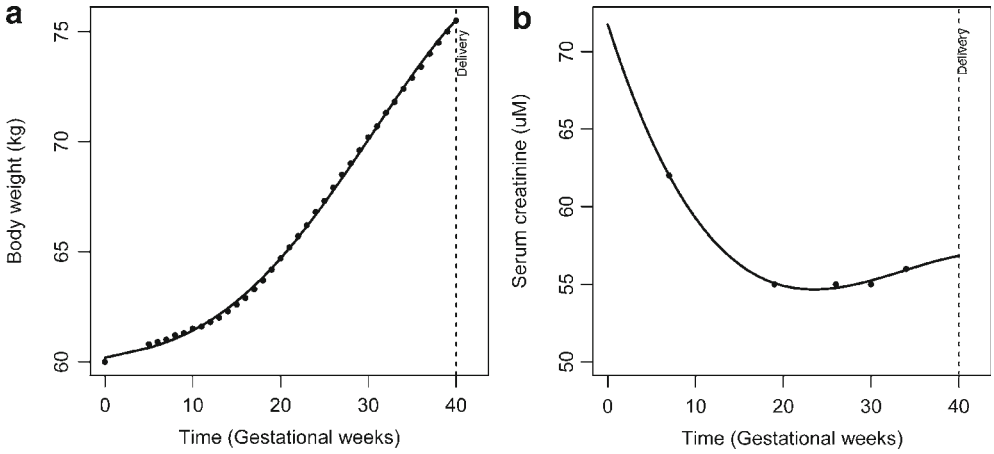

Fig. 2 Mean change in body weight (kg) and serum creatinine (uM) over time (gestational weeks). The *solid lines* represent the fit of the developed regression equations. The *solid circles* represent the observed values as obtained from literature. The *solid gray lines* represents time of delivery.

similar to an empirical reference model developed with data collected during pregnancy (6), and was able to support development of an optimal sparse sampling regimen. This is of significance as the core structure of the literature-based model could be used to develop informative sampling designs for other drugs, where no alternate prior model exist to aid optimization.

The predicted anti-Xa peak and trough profiles over pregnancy were comparable between the literature-based and reference models, although some over-prediction of the peak Anti-Xa levels by the literature-based was evident. This occurred as the reference model includes a sudden change in CL for non-pregnant *versus* early-pregnant women. Another abrupt change is present for volume of distribution, which increases at 31 gestational weeks with 41%. These instantaneous changes are obviously not representative of physiology, but are likely to be a limitation of the reference model. In contrast, the literature-based model allows CL and V to change continuously across the duration of pregnancy. The mean peak anti-Xa levels as reported by another study by Casele *et al* (19) which also investigated enoxaparin PK during pregnancy, also showed values close to the predictions of the literature-based model, further adding to the validity of this model.

Overall, optimal sampling times determined using the reference model and the literature-based model were comparable. For both designs, the first and last optimal sampling time points were located at the pre-defined boundaries of possible sampling times, whereas the middle optimal sampling time point was slightly different between the literature-based

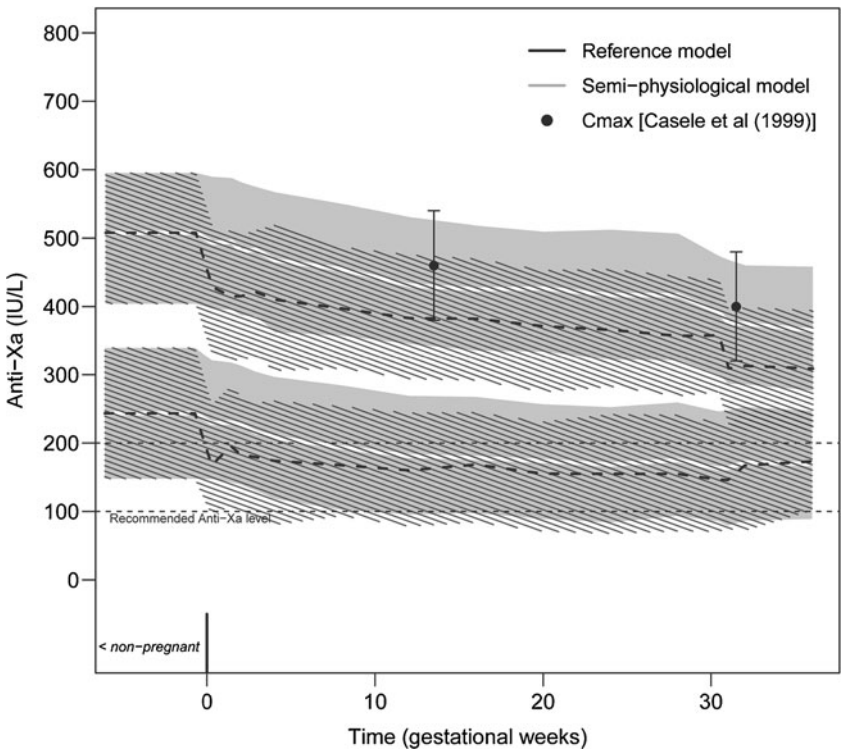

Fig. 3 Simulation (n=1,000) of peak and trough anti-Xa concentrations (median and 80% prediction interval) *versus* time (gestational weeks) using the literature-based model and the reference model. The *horizontal dashed lines* indicate the recommended range of minimum anti-Xa levels (15). The *solid circles* represent reported peak Anti-Xa values as reported by a second external study conducted by Casele *et al* (19).

Table IV D-optimal Sampling Times that were Obtained for the Literature-based Model and the Reference Model, at Different Sampling Occasions during Pregnancy. Three Sampling Times were Available at Each Occasion. Sampling Times are Depicted Around the Relative Time After Dose

Occasion (month)	Sampling times post dose (h)	
	Literature-based model	Reference model
0	−0.5, 0.585, 3.00	−0.5, 1.30, 3.00
2	−0.5, 0.585, 3.00	−0.5, 1.30, 3.00
4	−0.5, 0.585, 3.00	−0.5, 1.30, 3.00
6	−0.5, 0.585, 3.00	−0.5, 1.30, 3.00
8	−0.5, 0.585, 3.00	−0.5, 1.40, 3.00

model (0.585 h) and the reference model (1.30 h). Nonetheless, the D-optimal design developed from the literature-based model resulted in precise parameter estimation (RSE< 36.4%). Moreover, the precision of the parameter estimates obtained using the reference model was comparable to the literature-based model. Thus, the difference in the middle optimal sampling time point between models, did not show a significant impact on parameter precision. It may be postulated that substantial differences in sampling designs were not identify in part due to the limited design space that was available. However, the primary aim of this analysis was to evaluate sampling designs within the clinically feasible, practical boundaries of the anticipated study.

While there are some limitations to the material presented in this manuscript, the simple correlations made to the physiological variables CRCL and BW provided a reasonable prediction of pregnancy-changing PK. We recognise that the regression coefficients describing the changes WT and SCR have no physiological meaning by themselves, but they do provide a good prediction for the mean continuous change throughout pregnancy.

Since the physiological data is the driving force in predicting changes in PK parameters, the quality of these physiological variables is of pivotal importance. For instance, the pooled observed values of change in body water during pregnancy was highly variable. Although clear quality or method differences were not apparent in this case, it is important to decide carefully which literature data to include in the analysis.

While the need for a changing sampling design over pregnancy was not evident for enoxaparin, the need for a sampling time adaptation during pregnancy may still be relevant for other drugs or more complicated models. The requirements for sampling time adaptation is related to the magnitude of change in PK parameters during pregnancy and the model used as optimal design input. For enoxaparin, the maximum changes in CL and V were 60% and 27%, respectively. Although this is a substantial change from a clinical perspective, for estimation of parameters for a 1-compartmental model, change in optimal sampling times did not appear necessary. We encourage future work to understand when changing sampling designs are warranted, and explore how the physico-chemical properties of a drug impact the need for an adaptive sampling design over pregnancy. We do however propose that the methods used here for CRCL and BW are likely to be applicaple for other drugs with similar characteristics, i.e. those that remain within the intravascular space, are hydrophilic, and are predominantly renally cleared.

Similarly, we propose the methods may also be applicable to other scenarios with changing PK parameters, such as designs of pediatric clinical studies that include a wide age range (e.g. enzyme maturation), or clincal studies that assess different grade of renal or hepatic dysfunction.

Table V Precision and Bias of Sampling Designs for the Literature-based Model and the Reference Model, Obtained using Simulation (n=1,000) and Re-estimation of the Reference Model

Parameter	Sampling design			
	Literature-based model		Reference model	
Fixed effects	Precision (RSE%)	Bias (MRE%)	Precision (RSE%)	Bias (MRE%)
CL_{PR} (L/h)	4.47	1.66	4.51	1.45
V_{PR} (L)	6.13	0.16	6.30	1.58
K_A (h^{-1})	9.55	0.92	9.37	3.91
RATIO (−)	17.3	1.30	16.6	0.02
GEST (−)	8.72	0.38	7.54	0.27
Inter-individual variability				
CL (CV%)	36.0	8.39	36.4	7.06
V (CV%)	29.7	4.51	27.2	3.56
Residual variability				
Additive error (SD, IU/L)	4.65	0.73	4.58	0.77

CL_{PR} Clearance, V_{PR} Volume, K_A Absorption rate constant, RATIO Pregnancy covariate effect on clearance, GEST Pregnancy covariate effect on volume, MRE Mean relative error, RSE Relative Standard Error, CV Coefficient of variation

CONCLUSION

A literature-based model incorporating CRCL and BW to predict pregnancy-varying enoxaparin PK was sucessfully developed and applied to suport the development of an informative sampling design. Change in optimal sampling times over pregnancy was not found to be necessery, due to the moderate change in PK parameters for enoxaparin over time and the non-complex nature of the PK model (i.e. 1-compartment model, linear clearance). Regardless, we propose that the current framework, where literature information is leveraged, could be used for other drugs, for which informative sampling designs during pregnancy are to be developed.

REFERENCES

1. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. Clin Pharmacokinet. 2005;44:989.
2. Davison JM, Noble MCB. Serial changes in 24 hour creatinine clearance during normal menstrual cycles and the first trimester of pregnancy. Br J Obstet Gynaecol. 1981;88:10–7.
3. Dawes M, Chowienczyk PK. Pharmacokinetics in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2001;15:819–26.
4. Duffull S, Waterhouse T, Eccleston J. Some considerations on the design of population pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2005;32:441–57.
5. Andrew MA, *et al.* Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. Clin Pharmacol Ther. 2007;81:547–56.
6. Lebaudy, C. *et al.* Changes in enoxaparin pharmacokinetics during pregnancy and implications for antithrombotic therapeutic strategy. Clinical Pharmacology & Therapeutics (2008).
7. Andrew MA, Hebert MF, Vicini P. Physiologically based pharmacokinetic model of midazolam disposition during pregnancy. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2008;2008:5454–7.
8. Bergmann J-F, Mouly S. Thromboprophylaxis in medical patients: focus on France. Semin Thromb Hemost. 2002;28 Suppl 3:51–5.
9. Wong GC. Use of low-molecular-weight heparins in the management of acute coronary artery syndromes and percutaneous coronary intervention. JAMA. 2003;289:331–42.
10. Macklon NS, Greer I. Venous thromboembolic disease in obstetrics and gynaecology: the Scottish experience. Scott Med J. 1996;41: 83–6.
11. Pabinger I, Schneider B. Thrombotic risk in hereditary antithrombin III, protein C, or protein S deficiency. A cooperative, retrospective study. Gesellschaft fur Thrombose- und Hamostaseforschung (GTH) Study Group on Natural Inhibitors. Arterioscler Thromb Vasc Biol. 1996;16:742–8.
12. Friederich PW, *et al.* Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. Ann Intern Med. 1996;125:955–60.
13. Conard J, Horellou M, Van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies in AT III, protein C or protein S: study of 78 women. Thromb Haemost. 1990;63:319–20.
14. Green B, *et al.* Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. Br J Clin Pharmacol. 2005;59:281–90.
15. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N Engl J Med. 1996;335:108–14.
16. Frydman A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. Haemostasis. 1996;26:24–38.
17. Ensom MHH, Stephenson MD. Pharmacokinetics of low molecular weight heparin and unfractionated heparin in pregnancy. J Soc Gynecol Investig. 2004;11:377–83.
18. Greer I, Hunt BJ. Low molecular weight heparin in pregnancy: current issues. Br J Haematol. 2005;128:593–601.
19. Casele HL, Laifer SA, Woelkers DA, Venkataramanan R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. Am J Obstet Gynecol. 1999;181:1113.
20. Duffus GM, MacGillivray I, Dennis KJ. The relationship between baby weight and changes in maternal weight, total body water, plasma volume, electrolytes and proteins and urinary oestriol excretion. Int J Obstet Gynaecol. 1971;78:97–104.
21. Forsum E, Sadurskis A, Wager J. Resting metabolic rate and body composition of healthy Swedish women during pregnancy. Am J Clin Nutr. 1988;47:942.
22. Hytten FE, Thomson AM, Taggart N. Total body water in normal pregnancy. J Obstet Gynaecol Br Commonwealth. 1966;73:553–61.
23. Pipe NGJ, *et al.* Changes in fat, fat-free mass and body water in human normal pregnancy. Br J Obstet Gynaecol. 1979;86:929–40.
24. Davison JM, Hytten FE. Glomerular filtration during and after pregnancy. J Obstet Gynaecol Br Commonwealth. 1974;81:588–95.
25. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science (New York, NY). 1997;276:122–6.
26. Holford NHG. A size standard for pharmacokinetics. Clin Pharmacokinet. 1996;30:329–32.
27. Ochsenbein-Kolbe N, Roos M, Gasser T, Zimmermann R. Cross-sectional study of weight gain and increase in BMI throughout pregnancy. Eur J Obstet Gynecol. 2007;130:180–6.
28. Duffull SB, Dooley MJ, Green B, Poole SG, Kirkpatrick CMJ. A standard weight descriptor for dose adjustment in the obese patient. Clin Pharmacokinet. 2004;43:1167–78.
29. Beal SL, Boeckman AJ, Sheiner LB. NONMEM user guides. (1988).
30. Duffull SB, Denman N, Eccleston J, Kimko H. WinPOPT User Guide Version 1.2. (2008).