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Mechanistic Framework to Predict Maternal-Placental-Fetal Pharmacokinetics of Nifedipine Employing Physiologically Based Pharmacokinetic Modeling Approach

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Abstract

Nifedipine is used for treating mild to severe hypertension and preventing preterm labor in pregnant women. Nevertheless, concerns about nifedipine fetal exposure and safety are always raised. The aim of this study was to develop and validate a maternal-placental-fetal nifedipine physiologically based pharmacokinetic (PBPK) model and apply the model to predict maternal, placental, and fetal exposure to nifedipine at different pregnancy stages. A nifedipine PBPK model was verified with nonpregnant data and extended to the pregnant population after the inclusion of the fetoplacental multicompartment model that accounts for the placental tissue and different fetal organs within the Simcyp Simulator version 22. Model parametrization involved scaling nifedipine transplacental clearance based on Caco-2 permeability, and fetal hepatic clearance was obtained from in vitro to in vivo extrapolation encompassing cytochrome P450 3A7 and 3A4 activities. Predicted concentration profiles were compared with in vivo observations and the transplacental transfer results were evaluated using 2-fold criteria. The PBPK model predicted a mean cord-to-maternal plasma ratio of 0.98 (range, 0.86-1.06) at term, which agrees with experimental observations of 0.78 (range, 0.59-0.93). Predicted nifedipine exposure was 1.4-, 2.0-, and 3.0-fold lower at 15, 27, and 39 weeks of gestation when compared with nonpregnant exposure, respectively. This innovative PBPK model can be applied to support maternal and fetal safety assessment for nifedipine at various stages of pregnancy.

Keywords

fetus, nifedipine, PBPK, placenta, pregnancy

Pharmacotherapy during pregnancy is confined by the currently limited knowledge about fetal drug exposure and safety. In 1996, the following question was published in a specialized journal: Is the use of nifedipine during pregnancy safe for the fetus (adapted from Tadio et al[1])? Nifedipine has been extensively used in the treatment of mild to severe hypertension for pregnant women and as a tocolytic agent to prevent preterm labor.[2–4] Twenty-seven years have passed since then and there are still many questions to be answered on this topic. Administering nifedipine during pregnancy is believed to carry varying levels of teratogenic risks. These risks range from atrial septal defects and umbilical hernias when administered in the first trimester, as observed in animal models[5] and/or humans,[6,7] to minor birth defects such as slight dysplasia of the hip.[8,9] In addition, exposure to nifedipine during the third trimester of gestation is linked to an elevated risk of neonates developing jaundice and seizures.[7,10]

Different physiological changes take place during pregnancy, which can alter drug exposure.[11] Following multiple administrations of 20-mg nifedipine slow-release tablets every 12 hours, the area under the plasma concentration-time curve from time 0 to 12 hours in women at labor (120 ng•h/mL)[12] was found to be approximately 60% lower than in the nonpregnant population (300 ng•h/mL)[13] under the same dosing regimen. This decreased nifedipine exposure during

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pregnancy was largely attributed to the cytochrome P450 (CYP) 3A4 metabolism[14] that is induced during pregnancy reaching about 2.3-fold.[11] Nifedipine crosses the placental membrane with an umbilical cord-to-maternal plasma ratio ranging from 0.59 to 0.93.[12,15–19] It has been reported that the pharmacokinetics (PK) and placental transfer of nifedipine were similar when studied in 2 groups of pregnant women with hypertension during the third trimester with (n = 10) and without (n = 12) type 2 diabetes mellitus.[12] Nonetheless, due to ethical, logistical, and practical constraints, information regarding placental and fetal exposure to nifedipine during pregnancy is limited to the sampling of placenta, cord blood, and amniotic fluid at birth or when a diagnostic amniocentesis is performed.

Pregnancy physiologically based pharmacokinetic (PBPK) models, which encompass both drug-related parameters and the gestational age-dependent physiological parameters of the mother, placenta, and fetus, stand as a promising tool to investigate the influence of these physiological changes on drug exposure during pregnancy.[20] While the impact of these changes on maternal exposure has been demonstrated for different CYP3A4 substrates, including nifedipine[19,21,22] and relevant maternal physiological models have also been developed,[11] nifedipine transplacental and fetal exposure has not been assessed yet using the PBPK approach.

This study aimed to extend the previously published maternal nifedipine PBPK model to include the multicompartmental fetal and placental components and further apply the model to predict the maternal, placental, and fetal exposure to nifedipine at different stages of pregnancy upon administration of different formulations with different dosage regimens.

Material and Methods

Workflow

The Simcyp Simulator Version 22 (Certara) was used for all predictions of nifedipine PK in the pregnant population using the PBPK model workflow as depicted in Figure 1. The first step was the model building and validation using clinical data from the nonpregnant population. Subsequently, pregnancy-related physiological parameters and their variability between subjects were incorporated, as part of the virtual pregnancy population available with the Simulator. The physiological changes during pregnancy were incorporated into the model as continuous functions to allow predictions across various gestational ages.[11]

In this framework, the multicompartment fetal PBPK model is linked with the maternal PBPK model via a permeability-limited placenta model. Amniotic fluid was represented by a single compartment. The structure of the model, including underlying assumptions and equations, has been detailed in prior publications.[23,24]

Model Building

The default settings from the nifedipine compound file in the Simulator's compounds library were retained for the immediate release formulation. For the slow-release solid formulation, the established slow-dissolution profile was employed, as previously outlined.[11] The input parameters used for the nifedipine PBPK model can be found in Table S1. Before the integration of the fetoplacental and maternal PBPK models, the accuracy of the previously developed nifedipine PBPK model[11] predictions was verified in the nonpregnant population[25–27] (Table S1 and Figure S1).

To parameterize the maternal-placental-fetal model (details provided in Table S1), the placental permeability was estimated by scaling the nifedipine transplacental clearance (CL_{PD}) based on Caco-2 cell permeability studies. The nifedipine apparent permeability across Caco-2 cells (52.3×10^{-6} cm/s)[28] was used to estimate the effective permeability (5.39×10^{-4} cm/s). This value was further adjusted by the placental villi surface area[29] of 11.8 m^2 and then divided by the placental volume of 670 mL at term,[30] resulting in CL_{PD} of 0.33848 L/h/mL placenta. This CL_{PD} was used as a model input parameter for determining passive diffusion clearances on both sides of the placenta, under the assumption of a placental density of 1 g/mL.

To predict the amniotic fluid exposure to nifedipine, the fetal renal clearance (CL_R) was calculated using the fetal glomerular filtration rate (GFR) of 4.92 mL/min,[31] a typical adult GFR value of 121 mL/min,[32] fetal body weight at term of 3.5 kg (Simcyp default), and the adult nifedipine CL_R of 0.031 L/h (Simcyp default), using the following equation:

$$\text{Fetal } CL_R \text{ (L/h/kg)} = \frac{\text{Adult } CL_R \text{ (L/h)} \times \text{ Fetal GFR (mL/min)}}{\text{Fetal body weight (kg)} \times \text{ Adult GFR (mL/min)}}$$

The average volume of amniotic fluid swallowed by the fetus at term (400 mL/day)[33] was used to describe the swallowing activity clearance in the model (ie, $CL_{swallowing}$ = 0.0048 L/h/kg fetal body weight). Additionally, the intramembranous pathway transfers of fluid and solutes, approximately 350 mL/day from the amniotic cavity to the fetal circulation across the amniotic membranes, were incorporated into the model. The average flow rate was calculated using 350 mL/day and normalized to kilograms of fetal body weight at term (ie, $CL_{intramembranous}$ = 0.0044 L/h/kg). The fetal-to-amniotic clearance, composed of the sum of fetal

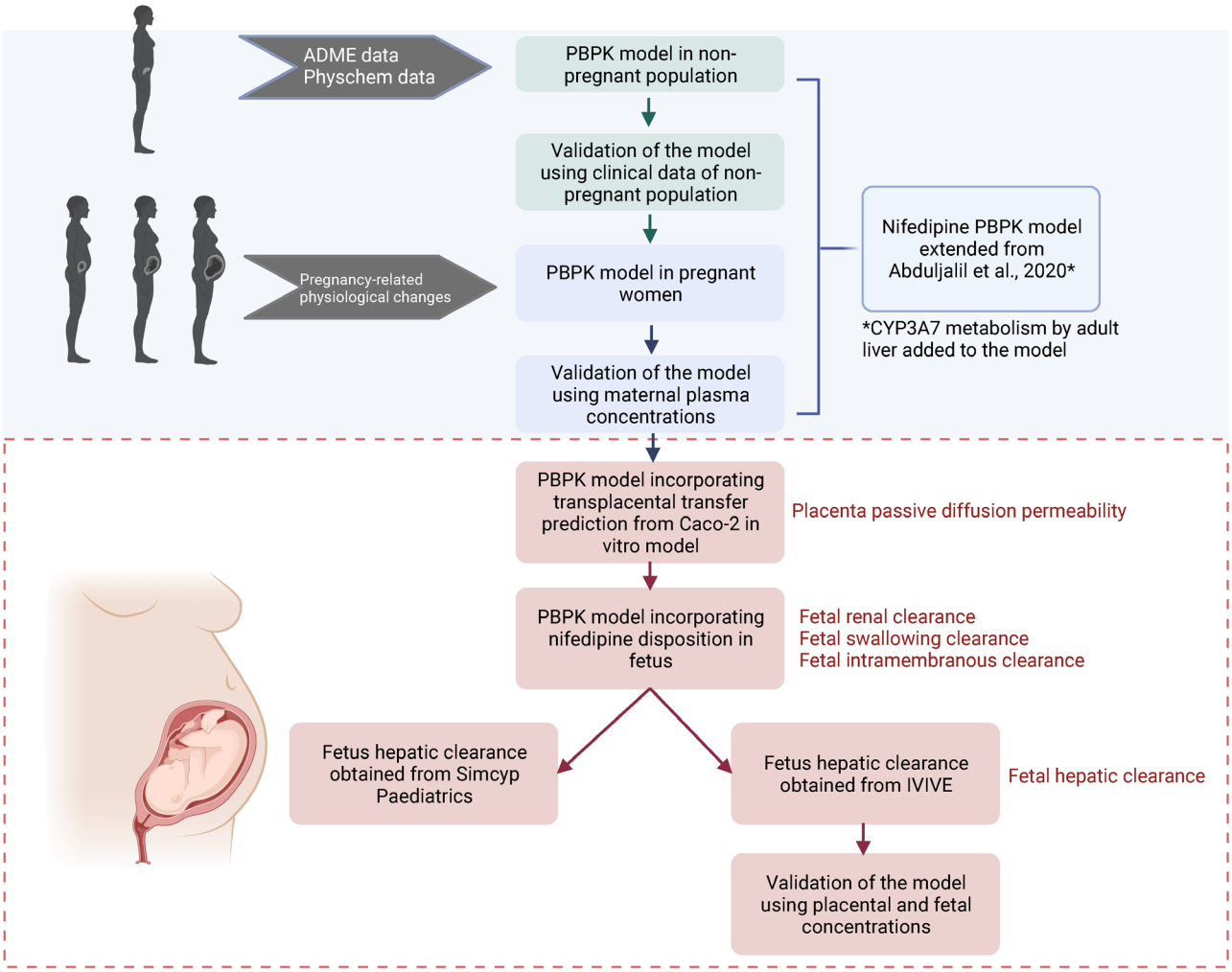

Figure 1. Nifedipine physiologically based pharmacokinetic (PBPK) model workflow. ADME, absorption, distribution, metabolism, and excretion; CYP, cytochrome P450; IVIVE, in vitro to in vivo extrapolation.

CL_R and $CL_{intramembranous}$, was incorporated into the model ($CL_R + CL_{intramembranous} = 0.005$ L/h/kg) (Table S1).

Two strategies were explored for predicting the hepatic fetal metabolism of nifedipine. The first one involved in vitro to in vivo extrapolation (IVIVE), while the second leveraged neonatal clearance at birth using pediatric population data within the Simcyp Simulator. For the IVIVE strategy, it was assumed that CYP3A7, CYP3A5, and CYP3A4 contributed to the metabolism of nifedipine by term fetuses (see Table 1). The in vitro maximum velocity (V_{max}) and Michaelis constant (K_m) values for CYP3A4 and CYP3A5 were taken from the Simcyp nifedipine file as they have been combined from different experiments (see Table S1). As for CYP3A7, published in vitro values for V_{max} and K_m from recombinant CYP3A7 isoform (Williams et al[14]) were used in the calculation of total hepatic intrinsic clearance and scaled up to the fetal hepatic clearance ($CL_{H,fetus}$) according to the following equations:

$$V_{max_{corr}}\ (\text{pmol/min/pmol CYP3A7}) = Vmax_{\text{in-vitro}}\ (\text{pmol/min/pmol CYP3A7}) \times ISEF_{CYP3A7}$$

$$Km_{corr,CYP3A7}\ (\mu M) = K_{m_{CYP3A7,\ \text{in-vitro}}} \times fu_{mic}$$

$$V_{max,fetus,CYPi}\ (\mu\text{mol/h}) = V_{max,\ corr} \times CYP_{abundance\ fetus} \times MPPGL_{fetus} \times LivWt_{fetus} \times \left(\frac{60}{1000000}\right)$$

$$CL_{int}\ (\text{L/h}) = \frac{V_{max,\ fetus,CYP3A4}}{K_{m,\ corr,CYP3A4}} + \frac{V_{max,\ fetus,CYP3A5}}{K_{m,\ corr,CYP3A5}} + \frac{V_{max,\ fetus,CYP3A7}}{K_{m,\ corr,CYP3A7}}$$

Table 1. In Vitro to In Vivo Extrapolation to Nifedipine Fetal Metabolism

Parameter	CYP3A7	CYP3A4	CYP3A5	Reference
$K_{m,rhCYP}$ (μM)	34	9.11	30.29	Williams et al[14]; Simcyp Default
$V_{max,rhCYP}$ (nmol/min/nmol P450)	2	17.88	23.05	Williams et al[14]; Simcyp Default
CYP abundance in the fetus (pmoLCYP/mg microsome)	359	5	15	Shum et al[34], Stevens et al[35], Quinney et al[22]
$V_{max,fetus}$ (μmoL/h)	58.0	18.3	70.9	Calculated
ISEF	0.044	1	1	Shum et al[34] for CYP3A7, value assumed for 3A4 and 3A5
CL_{int} (L/h)	2.0	2.0	2.3	Calculated
$CL_{H,fetus}$ (L/h/kg)	0.14	0.14	0.16	Calculated

CL_H, hepatic clearance; $CL_{int,u}$, intrinsic clearance unbound; CYP, cytochrome P450; ISEF, intersystem extrapolation factor; K_m, Michaelis constant; rhCYP, recombinant human isoforms; S_{50}, constant for sigmoidal kinetics that represents the substrate concentration at which 50% of V_{max} is achieved; V_{max}, maximum velocity.

$$CL_{H,fetus}\,(L/h/kg) = \frac{Q \times f_{uB} \times CL_{int,fetus}}{Q + f_{uB} \times CL_{int,fetus}} \times \frac{1}{\text{Body weight}_{fetus}}$$

$V_{max,in\text{-}vitro}$ is the in vitro maximal reaction velocity, $ISEF_{CYP3A7}$ is an intersystem extrapolation factor (ISEF) for CYP3A7 of 0.044 obtained from Shum and Isoherranen,[34] $CYP_{abundance,\,fetus}$ is the amount of CYP isoenzyme in the fetal liver and set to 5, 15, and 297 pmol/mg microsomal protein for CYP3A4,[35] CYP3A5,[35] and CYP3A7,[34] respectively. The amount of microsomal protein in milligrams per gram of fetal liver ($MPPGL_{fetal}$) was set to 23.25 mg protein/g liver (average of published values reported in Shum and Isoherranen[34] and Pelkonen et al[36]). The $V_{max,rhCYP}$ and CYP abundance in fetus values are demonstrated in Table 1. Fetal liver weight of 147 g in term neonates weighing 3.5 kg is the calculated value within the Simcyp Simulator.[37] The fetal hepatic fu_{mic} is the fraction unbound in microsome (calculated using Simcyp calculator), $f_{uB,fetal}$ is nifedipine fraction unbound in fetal blood of 0.07 (calculated within the Simulator by dividing fetal plasma fraction unbound by fetal blood to plasma ratio). Q_{fetal} is the fetal hepatic flow of 17.0 L/h for the fetus at term calculated within the simulator.[38] The total $CL_{H,fetus}$ calculated through IVIVE was 0.13 L/h/kg fetal weight.

The second strategy to achieve $CL_{H,fetus}$ was using the predicted neonatal CL_H at birth (Simcyp Pediatric Simulator) obtained for a single intravenous dose of nifedipine 5 mg administered to virtual subjects (N = 200 neonates; 50% female) aged 0 years. The obtained mean CL_H was 0.14 L/k/kg body weight, so this value was used as input for $CL_{H,fetus}$.

The nifedipine transplacental transfer PBPK model was validated by comparing simulated trials against clinical studies using the same study design. The clinical studies and the information used to set the simulated trials are depicted in Table 2. The virtual pregnancy population within the Simcyp Simulator was used to replicate clinical studies during pregnancy using the mean gestational week (GW) or GWs range if a wide range is reported in the study. The disease status was not considered for the performed simulations in the current work.

The PBPK model predictions were deemed successful and acceptable when the observed PK profile was within the 5th and 95th percentiles of predicted data, and the predicted PK parameters aligned within a range of 0.5- to 2-fold in comparison to the observed data.

Results

The PBPK model predictions, aligned with available observations, show nifedipine concentration profiles in maternal plasma during delivery, as depicted in Figure 2. Additionally, Figure 2 shows the predicted nifedipine concentration profiles in the amniotic fluid, umbilical vein (UV), and the placental intervillous space during delivery according to the observed data. Table 3 provides a comparison of the predicted nifedipine transplacental transfer parameters with the observed data from clinical studies.

The mechanistic placental model of passive transplacental transfer (CL_{PD}) of nifedipine using Caco-2 permeability resulted in predicted nifedipine umbilical concentrations that closely resembled the observed concentrations in clinical studies (Figure 2, Plots 1B, 2B, 3B, 4B, 5B, and 6B), indicating a UV-to-maternal vein (UV/MV) ratio close to the unity.

Accounting for nifedipine's fetal metabolism using either full-term metabolic clearance at birth (data not shown) or using the IVIVE approach to scale in vitro data based on fetal liver yielded similar and accurate descriptions of the observed nifedipine fetal concentrations data. Ultimately, the IVIVE approach based on scaled fetal data was selected.

The model prediction for nifedipine in maternal blood within the placenta describes the observed values for nifedipine intervillous space concentrations

Table 2. Demographic Characteristics Extracted from Clinical Trial Articles Used in the Validation of the Nifedipine PBPK Model

Trial design	Reference	n	Age (years)	GW	Patients	Formulation	Dosage regimen	Samples
1	Filgueira et al[12] (raw data)	22	20-46	34-39.6 (third trimester) 34-40.1 (delivery)	Hypertensive and/or diabetic	Slow-release tablet	20 mg twice daily	MV, UV, UA, AF, IS, MC
2	Manninen and Juhakoski[15]	11	23-38	31-39 (36)	Hypertensive	Tablet	10 mg 3 times daily	MV, UV, AF
3	Ferguson et al[16]	12	26.4 ± 5.3	29.7 ± 4	Preterm labor	Sublingual tablet	20 mg sublingual dose 3 times daily	MV, UV
4	Silberschmidt et al[17]	40	30.6 ± 5.8	34.7 ± 0.8 (delivery)	Preterm labor	Gastrointestinal therapeutic system tablet	30 mg 3 times daily[a]	MV, UV
5	Pirhonen et al[18]	10	19-33	38.8 (37-39)	Normotensive participating in the Doppler study	Tablet	20 mg single dose	MV, UV
6	Prevost et al[19]	15	15-34	32.1 (26-35)	Hypertensive	Tablet	10 mg 4 times daily	MV, UV, AF
7	Papatsonis et al[39]	5	29.5 ± 4.5	31.3 ± 0.9	Preterm labor	Capsule/slow-release tablet	10 mg oral capsules each 15 minutes during 60 minutes (4 doses) (load dose), then 1 slow-release tablet 20 mg at time 90 minutes	MV
8	Marin et al[40]	24		22-34[b] (second and third trimesters)	Preterm labor	Capsule/slow-release tablet	10 mg oral dose capsules each 15 minutes during 60 minutes (4 doses) (load dose) then 1 slow-release tablet 60 mg	MC

AF, amniotic fluid; GW, gestational week; IS, intervillous space; MC, maternal concentrations during third trimester; MV, maternal vein during delivery; PBPK, physiologically based pharmacokinetic; UA, umbilical artery; UV, umbilical vein; UV:MV ratio, umbilical vein-to maternal vein ratio at delivery.

[a]The patients had different dosage regimens varying from 30 to 150 mg/daily (each 6, 8, or 12 hours), the mean dose reported (94 mg/daily) was used for simulation.

[b]Second and third trimesters of gestation were simulated using multiple populations in Simcyp Simulator.

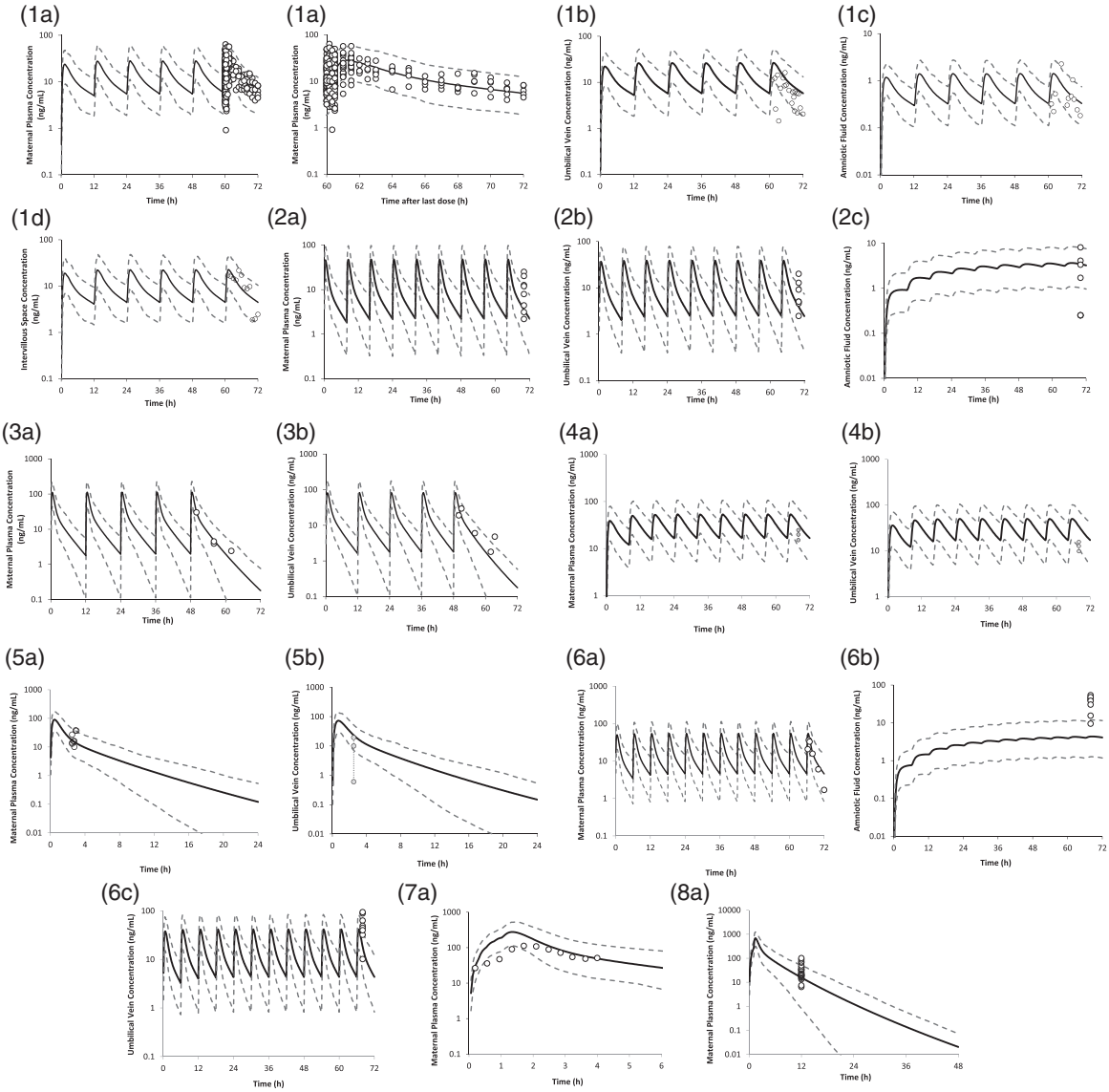

Figure 2. Maternal-placental-fetal nifedipine concentration profiles after oral administration of nifedipine. Solid lines, predicted means; dashed lines, 5th and 95th centiles; closed circles, individual observations; closed circles filled with gray, observed mean and standard deviation. Plots 1, Trial Design 1 (Filgueira et al[12] raw data); Plots 2, Trial Design 2 (Manninen and Juhakoski[15]); Plots 3, Trial Design 3 (Ferguson et al[16]); Plots 4, Trial Design 4 (Silberschmidt et al[17]); Plots 5, Trial Design 5 (Pirhonen et al[18]); Plots 6, Trial Design 6 (Prevost et al[19]); Plot 7, Trial Design 7 (Papatsonis et al[39]); Plot 8, Trial Design 8 (Marin et al[40]). (a) Maternal plasma concentration; (b) umbilical vein concentration; (c) amniotic fluid concentration; (d) intervillous space concentration. See the Materials and Methods section for trial settings.

(depicted in Figure 2, Plot 1D). Regarding the predicted nifedipine concentrations in the amniotic fluid, the model matched observations from 1 study (Figure 2, Plot 2C), yet it either underestimates (as seen in Figure 2, Plot 6C) or overestimates (Figure 2, Plot 1C) the values from other clinical studies.

Discussion

Regardless of recent advancements in clinical obstetric pharmacology studies, gaps persist in comprehending maternal and fetal drug exposure. The present work describes the development and application of an intricate maternal-placental-fetal PBPK model to predict maternal and fetal nifedipine exposure upon administration of immediate or modified-release formulations. First, predicted nifedipine PK parameters were within a 2-fold range of the observed values in the nonpregnant population. Moreover, the observed concentration profiles were captured within the predicted 5th and 95th percentiles for the systemic exposure profiles in plasma (Figure S1 and Table S2).

Validation of the combined maternal-placental-fetal nifedipine PBPK model was conducted using data

Table 3. Mean Predicted versus Observed Nifedipine Transplacental Transfer Data

Trial design	1	2	3	4	5	6
Parameter[a] reference	Filgueira et al[12]	Manninen and Juhakoski[15]	Ferguson et al[16]	Silberschmidt et al[17]	Pirhonen et al[18]	Prevost et al[19]
($AUC_{UV/MV\ obs}$)	0.59	0.70	0.91	0.77	0.76	0.93
$AUC_{UV/MV\ pred}$	1.02	1.02	0.86	0.99	1.06	0.91
Ratio	0.58	0.69	1.06	0.78	0.72	1.02
$AUC_{AF/MV\ obs}$	0.050	0.20	NA	NA	NA	0.56
($AUC_{AF/MV\ pred}$)	0.056	0.31	NA	NA	NA	0.25
Ratio	0.89	0.65	NA	NA	NA	2.24
$AUC_{IS/MV\ obs}$	0.85	NA	NA	NA	NA	NA
$AUC_{IS/MV\ pred}$	0.81	NA	NA	NA	NA	NA
Ratio	1.04	NA	NA	NA	NA	NA

AF, amniotic fluid; AUC, area under the plasma concentration-time curve; $AUC_{UV/MV\ obs}$, observed umbilical vein to maternal vein area under the curve ratio; $AUC_{UV/MV\ pred}$, predicted umbilical vein to maternal vein area under the curve ratio; IS, intervillous space; MV, maternal vein during delivery; NA, not applicable; obs, observed mean; pred, predicted mean; UA, umbilical artery; UV, umbilical vein.

[a] AUC data were used when available; in other cases, the ratio values reported in the study were considered for the observed data.

extracted from 9 clinical studies reporting maternal plasma concentrations, 6 studies reporting UV plasma concentrations, 3 studies reporting amniotic fluid concentrations, and 1 study reporting intervillous space concentrations (Table 2). Predicted versus observed nifedipine concentration-time profiles and PK parameters in the maternal and umbilical cord at delivery are given in Figure 2 and Table 3, respectively. The UV/MV nifedipine ratio in plasma based on the area under the plasma concentration-time curve predicted was 0.98 (0.86-1.06), which agrees with the observed ratio based on the drug plasma concentration at delivery of 0.78 (0.59-0.93). The observed UV/MV ratio data are variable, for example, the average ratio from Prevost et al[19] is 1.6 higher than the average ratio reported by Filgueira et al.[12]

The CL_{PD} obtained from the Caco-2 cells approach was selected for the nifedipine maternal-placental-fetal PBPK model building for demonstrating an alternative approach of integrating permeability cell line data for the placental membrane. It would be ideal to use permeability data for nifedipine using a placenta-derived cell line. However, such information is not available. An attempt was also performed to include transplacental clearance reported from an ex vivo cotyledon perfusion experiment of 0.0324 L/h,[41] but this value resulted in a very low ex vivo transfer of 5%, which does not match the observed in vivo listed in Table 3.

Results obtained from accounting for nifedipine fetal metabolism in the model using either full-term metabolic clearance at birth (data not shown) or using the IVIVE approach to scale in vitro data based on fetal liver were similar and adequately described the observed nifedipine umbilical concentrations. Since the IVIVE approach is based on scaled fetal data, it was retained in the model. Nifedipine in vitro oxidation by CYP3A recombinant human isoforms is in the following order CYP3A4 >>> CYP3A5 >> CYP3A7.[14] Despite CYP3A4 being the predominant form expressed in adults,[35] CYP3A7 is expressed in the fetus liver and decreases with the progression of gestation, achieving the levels of 311 and 160-201 pmoL/mg fetal microsomal protein in the second and third trimesters of gestation, respectively.[35,42] However, it should be noted that the contribution of fetal nifedipine metabolism to the overall drug metabolism in the maternal system can be considered negligible due to small fetal liver size. The calculated fetal metabolism clearance at term was 0.45 L/h, which is approximately 0.5% of the maternal clearance of 89.2 L/h.[23] No effort was made to assess the role of intestinal metabolism in the current model as the gut CYP3A activity was found to be approximately 30% of the liver CYP3A activity in neonates.[43]

Nifedipine intervillous space concentrations are about 80% of the MV concentrations, which is expected since it is in direct contact with maternal blood. Model predictions well described these observations as shown in Figure 1, Plot 1D. Nifedipine can reach amniotic fluid by different passive mechanisms including the flux of the fluid through the membrane, placenta, fetal skin, and lung, and through fetal urination, with the latter being the main pathways. The developed model considered multiple pathways, but not all, based on available data.[23] The observed nifedipine amniotic fluid-to-maternal plasma concentration ratio at steady state was highly variable (0.050-0.56). The model predictions were well agreed with those reported by Filgueira et al[12] and Manninen and Juhakoski,[15] but lower than those observed by Prevost et al.[19]

Expanding the scope of the nifedipine pregnancy PBPK model applications, the scenarios of maternal and fetal nifedipine concentrations at the 15th, 27th, and 39th GWs (Figure 3) were simulated using the

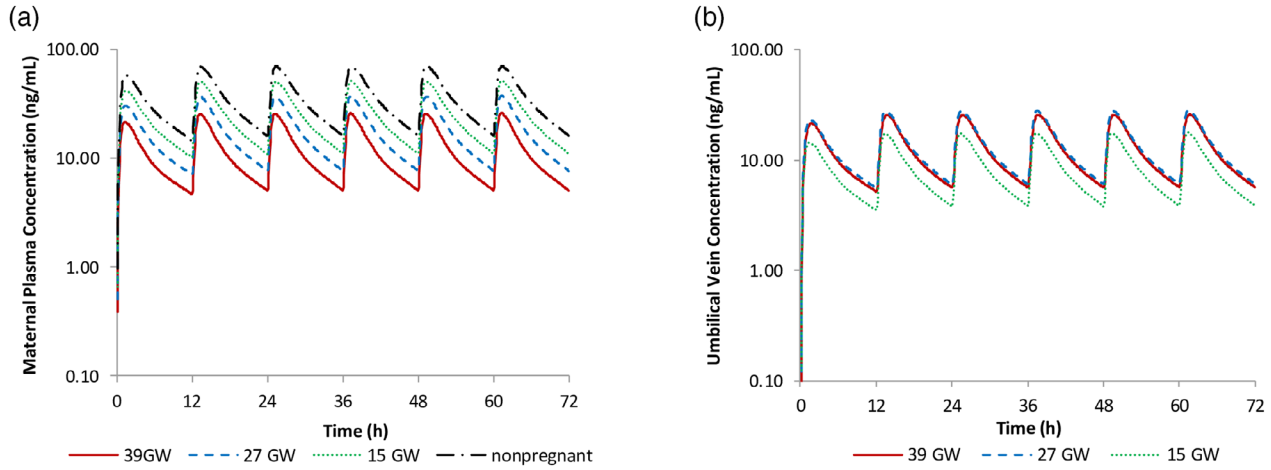

Figure 3. Predicted mean maternal (a) and umbilical (b) plasma nifedipine concentration profiles after 20 mg twice-daily oral slow-release nifedipine tablets to pregnant women at 15th (green dotted line), 27th (blue dashed line), and 39th (red solid line) GWs. The black dashed-dotted line represents the mean plasma concentration in nonpregnant women under the same dosage regimen. GW, gestational week.

same study design of Filgueira et al[12] (Trial Design 1). The maternal plasma concentrations decreased with the increase of GWs due to the increase of CYP3A4 activity during pregnancy.[11] The UV concentrations were similar between the 27th and 39th GWs as the placenta permeability to nifedipine increases with pregnancy progression. This ratio is higher than in earlier pregnancy (15th GW) when the placenta is less permeable despite the maternal nifedipine gradient levels at these GWs (Figure 3). The combined main effects of the increasing maternal elimination and increasing placenta permeability (with little contribution from the increasing fetal elimination), the mean (± standard deviation) predicted umbilical/maternal ratios were 0.35 ± 0.07, 0.78 ± 0.16, and 1.09 ± 0.23 at 15, 27, and 39 GWs, respectively.

While the nifedipine model has been developed and integrated with different compound and physiological parameters, there are still a few limitations to be addressed. There was a lack in the provided information in the published studies about the brand and dissolution data of each nifedipine formulation. For Clinical Studies 1, 4, 7, and 8, there was an indication that the formulation was either controlled- or slow-release; a slow-release option in the model was used. For Clinical Studies 2, 3, 5, and 6, the solution option in the model was used as those studies either mentioned the use of immediate-release formulation or no details were available (Table S1). For multiple-dose simulations, a fixed time at steady state was assumed to compare with the observed results since there was a lack of treatment durations in the clinical studies. For the remaining clinical trials, the same study period of the clinical study was used in the simulation. Figure 1a demonstrates the multiple-dose treatment followed by the last-dose treatment for better data visualization. It was not possible in the current features of the Simulator to replicate the trial design where the first administered formulation was a fast-release and the second dose was a slow-release formulation (Trials 7 and 8), for these cases, simulations were executed for the slow-release formulation for which nifedipine concentrations were reported. The transplacental transfer in the developed nifedipine PBPK model was assumed to be a passive diffusion mechanism. Published studies showed that nifedipine is a substrate of breast cancer resistance protein transporter,[44–46] but not a substrate of P-glycoprotein.[47,48] Accounting for the transporter kinetics may improve the slight overprediction of the UV/MV ratio. Nevertheless, such data are still not available. In the IVIVE approach for predicting nifedipine fetal metabolism, the ISEF for CYP3A4 and CYP3A5 were set as unity (ISEF = 1) due to the lack of nifedipine in vitro metabolism data by human fetal liver in the third trimester of gestation, while the ISEF for CYP3A7 was set as 0.044 based on data from Shum and Isoherranen.[34] Furthermore, samples obtained from fetal-placental units are not available before delivery, so verification of the model prediction during earlier GWs were not feasible. The variability in UV/MV ratio measurements could be either due to sampling procedures or the fact that the efflux transporter was induced by medications, which were not provided in the published studies.

The developed nifedipine PBPK model can be used to predict placental and different fetal organ exposures after maternal administration of immediate or modified release formulations, which were limitations in the previously published model.[11,22,49,50] A fundamental aspect of fetal pharmacology is that of the amount (and rate) of the drug reaching the fetus. The drug transfer to the fetus determines the presence or absence

of pharmacologic or toxic effects. The model can be used to assess the fetal exposure scenarios where maternal exposure is altered due to comedication, dose or formulation modifications, and changes in maternal physiology due to comorbidity that can affect the normal kinetics of nifedipine. Generating such information for clinicians can help to address the current gap between nifedipine maternal and fetal exposure and neonatal outcomes.[2,4,51]

In conclusion, a detailed mechanistic PBPK model has been developed in this work to predict the maternal-placental-fetal PK of nifedipine. The model can provide insight into the nifedipine placental and fetal exposure helping to better understand the mechanisms of nifedipine distribution and elimination within the fetal-placental unit. By combining the current model with response and safety data, we could support precision dosing strategies based on maternal-fetal exposure. Continuous enhancement of this "live" PBPK model depends on future in vitro, ex vivo, and in vivo studies that can be used to fill any knowledge gaps regarding transfer mechanisms to improve the confidence in the model.

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Author Contributions

Conceptualization: F.L.M.; methodology: M.A.W.R., F.L.M.; validation: M.A.W.R., F.L.M.; formal analysis: M.A.V.R.., F.L.M., K.A., L.P.; N.V.M.; investigation: R.C.C., G.D.; resources: F.L.M.; writing—original draft: F.L.M.; writing—review and editing: K.A., L.P., R.C.C., G.D., N.V.M.; supervision: F.L.M., K.A.; project administration: F.L.M.

Conflicts of Interest

Marya Antônya Werdan, Leonardo Pinto, Ricardo Carvalho Cavalli, Geraldo Duarte, Natália Valadares de Moraes, and Fernanda de Lima Moreira declare no conflict of interest. Khaled Abduljalil is an employee of Certara UK Limited and may hold shares in Certara.

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Data Availability Statement

The original contributions presented in the study are included in the article/Supplemental Information. Further requests can be directed to the corresponding author.

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Supplemental Information

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