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BACKGROUND

The pharmacokinetics (PK) of long-acting (LA) injectable cabotegravir (CAB) and rilpivirine (RPV) have not been prospectively studied in pregnancy. Physiologically-based pharmacokinetic models (PBPK) offer the ability to incorporate physiologic pregnancy-associated changes and drug specific characteristics to predict the concentration exposure during pregnancy before concentration measurements are made. We hypothesized that pregnant individuals who initiate CAB LA and RPV LA in the beginning of the 2nd trimester would have lower systemic exposure in the 2nd and 3rd trimester than non-pregnant cisgender women due to the physiologic changes of pregnancy.

METHODS

We used a published maternal-fetal PBPK model by Dallmann et. al. in Open Systems Pharmacology to predict concentrations of CAB LA and RPV LA in cisgender women during their 2nd and 3rd trimesters of pregnancy.¹ This model was previously used to predict the maternal PK of Dolutegravir and Raltegravir and to verify the induction of UGT1A1 and CYP3A4 during the 2nd and 3rd trimesters.²

We obtained drug specific parameters for CAB LA and RPV LA from the published literature³ and used published clinical PK data for CAB and RPV (oral and IM) in nonpregnant, cisgender women to validate the nonpregnant PBPK model.⁴⁻⁶ The parameters used for simulation is summarized in Table 1.

We then extended the validated model to pregnancy and the PBPK model was utilized to simulate dose sequences in nonpregnant and pregnant individuals who initiate CAB LA and RPV LA in the early 2nd trimester, including a loading dose paradigm, with monthly dosing up to 6 months. We estimated the placental diffusion clearance of CAB LA and RPV LA from MDCK and Caco-2 Permeability.⁷ The fraction unbound was calculated using the mean albumin level measured during each trimester.² Pregnancy-mediated induction of UGT1A1 and CYP3A4 was incorporated.

RESULTS

The physiochemical and PK parameters of CAB and RPV are reported in Table 1. The ratio of simulated to observed PK parameters in nonpregnant individuals are shown in Table 2. The simulation results using the maternal-fetal PBPK model is shown in Figure 1. We assume the first 3 doses were injected during the 2nd trimester and the last 3 doses were injected during the 3rd trimester. According to the simulation results, the trough concentrations after the 1st injection (loading dose) were 29.5% and 23.0% lower during pregnancy compared to outside of pregnancy for CAB LA and RPV LA, respectively. The trough concentrations after the 6th injection were 31.1% and 29.2% decreased for CAB LA and RPV LA, respectively.

- Our maternal-fetal PBPK model predicts a reduction in plasma concentrations during the 2nd and 3rd trimesters among individuals who initiate CAB LA and RPV LA in pregnancy

- This prediction underscores the need for prospective clinical trials of CAB LA and RPV LA in pregnancy to evaluate the pharmacokinetics in the 2nd and 3rd trimesters

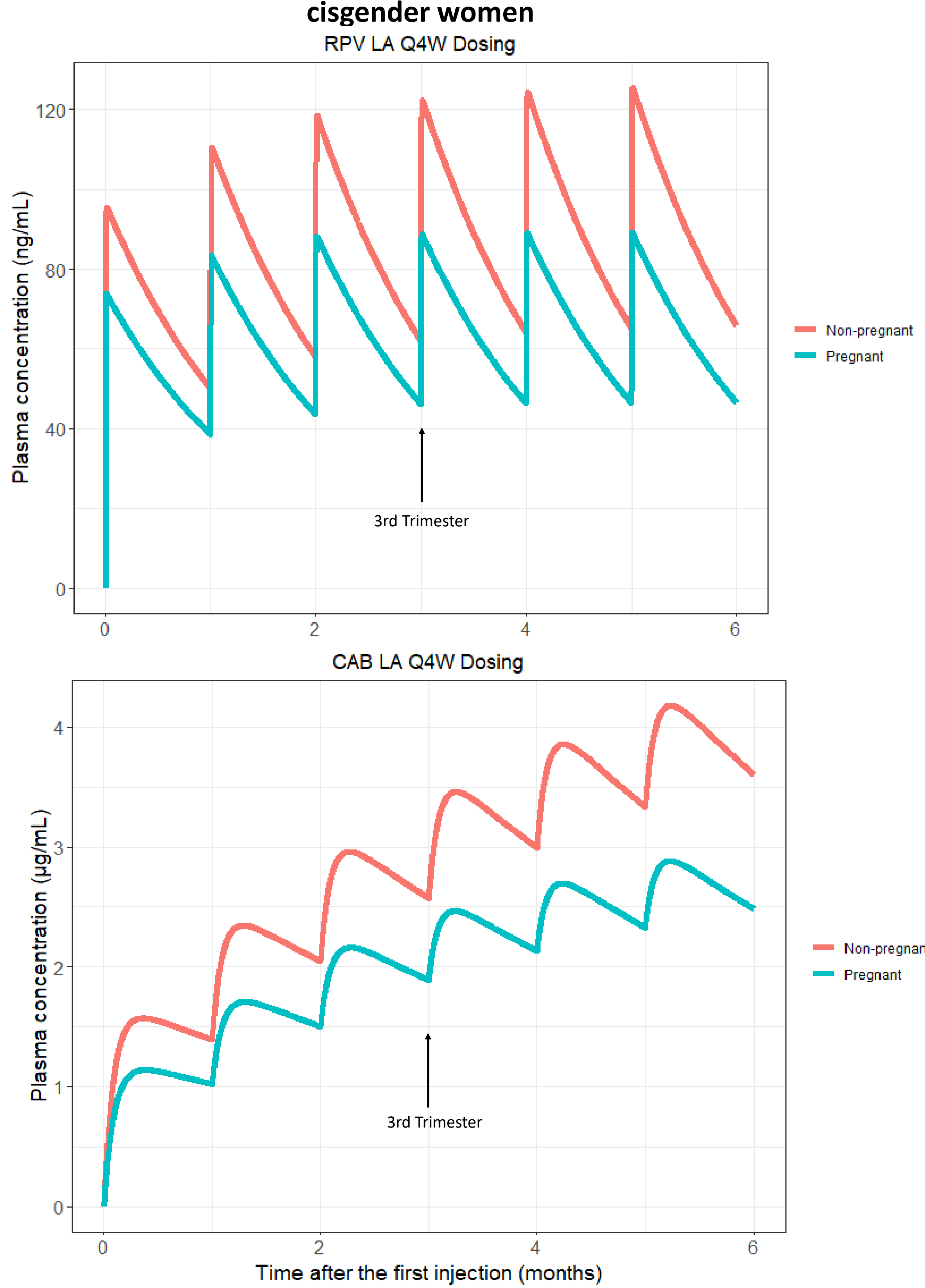
Table 1 Physicochemical properties and pharmacokinetic parameter of Cabotegravir and Rilpivirine

Cabotegravir Parameters	Value
Molecular Weight	427
Log P	1.04
Protein binding	99.3%
pKa	10.04
Km/Vmax UGT1A1(uM,pmol/min/mg)	148 / 660
Km/Vmax UGT1A9(uM,pmol/min/mg)	90 / 200
Release rate (/h)	0.0003
Major binding protein	Albumin
MDCK permeability (nm/sec)	256
Rilpivirine Parameters	
Molecular Weight	366
Log P	4.32
Protein binding	99.7%
pKa	3.26
CLint CYP3A4(uL/min/pmol)	2.04
Release rate (/h)	0.0009
Major binding protein	Albumin
Caco-2 permeability (cm/sec)	12×10 ⁻⁶

Table 2 Comparison of simulated and observed pharmacokinetic parameters in non-pregnant cisgender women

	AUC0-t (mg*h/L)	Cmax (mg/L)	tmax (h)
	Simulated/observed (ratio)	Simulated/observed (ratio)	Simulated/observed (ratio)
Rilpivirine			
25mg oral steady state	2.31/2.25 (0.92)	0.18/0.15 (1.20)	170/172 (0.99)
1200mg IM + 900mg IM	218/206 (1.06)	0.16/0.15 (1.07)	682/792 (0.86)
Cabotegravir			
30mg oral	194/126 (1.54)	2.62/3.48 (0.75)	5.25/2.12 (2.47)
100mg IM	785/820 (0.96)	0.26/0.24 (1.08)	294/210 (1.40)
200mg IM	1570/1240 (1.27)	0.52/0.31 (1.68)	294/815 (0.36)
400mg IM	3430/2870 (1.20)	1.04/0.68 (1.53)	294/1663 (0.18)
800mg IM	6010/6150 (0.98)	2.08/3.83 (0.54)	294/133 (2.21)

Figure 1 Comparison of simulated pharmacokinetic profiles in non-pregnant cisgender women and pregnant



CONCLUSIONS

This maternal-fetal PBPK model predicts a reduction in plasma concentrations in pregnancies who initiate CAB LA and RPV LA in the beginning of 2nd trimester, attributed to the predicted induction of UGT1A1 and CYP3A4 during the 2nd and 3rd trimesters.

There are insufficient clinical data for CAB LA and RPV LA in pregnancy populations, indicating the importance of clinical trials to further evaluate the pharmacokinetics in the 2nd and 3rd trimesters.

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