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Precision dosing of venlafaxine during pregnancy: a pharmacokinetics modelling approach

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Abstract

Objectives: Venlafaxine exposure through gestation is affected by the longitudinal changes in maternal physiology. Confounding treatment is also the impact of CYP2D6 polymorphisms affecting plasma concentrations of venlafaxine.

Methods: A pharmacokinetic modelling approach was employed to assess variations in maternal and foetal cord venlafaxine levels throughout gestation and to identify appropriate doses to maintain venlafaxine levels within the therapeutic range.

Key findings: Throughout gestation, there was a significant decrease in simulated venlafaxine trough plasma concentrations in both extensive metaboliser (EM) and ultra-rapid metaboliser (UM) phenotypes. Approximately 70%–87% of EM and UM phenotypes exhibited trough venlafaxine plasma concentrations below the therapeutic level (<25 ng/ml), which increased to 96% at week 30. While for poor metabolizer (PM) phenotypes, the percentage was approximately 4%.

Conclusion: The standard daily dose of 75 mg required adjustment for all phenotypes examined during gestation. A daily dose of 37.5–112.5 mg is appropriate for PM throughout pregnancy. For EM, a dose of 225 mg daily in the first trimester, 262.5 mg daily in the second trimester, and 375 mg daily in the third trimester is suggested to be optimal. For UM, a dose of 375 mg daily throughout gestation is suggested to be optimal.

Keywords: pharmacokinetics; physiologically-based pharmacokinetics; pregnancy; precision dosing; mental health

Introduction

Globally, depression is considered the most common psychiatric disorder [1] and has been classified as the third greatest contributor to worldwide illness burden [2]. Women are twice as likely to experience depression compared to men [3], and often their first symptoms of major depression occur during their childbearing years [4]. Approximately 20% of pregnant and postpartum women suffer from depressive disorders [5]. Pregnancy is challenging for women with a history of mental health issues and untreated depression during pregnancy may result in poor self-care, inability to follow prenatal recommendations, suicidality, and impulsivity, all of which can put the health of the mother and the foetus at risk [6, 7].

Confounding pharmacological interventions for depression during pregnancy are maternal physiological changes through gestation that may alter the extent of clinical outcomes during treatment. Changes are variable and include alterations in (i) gastric acid production, altering the ionization of drugs [8]; (ii) changes in the cardiovascular system affecting drug distribution [9]; (iii) redistribution of body water/fat during all stages of pregnancy enhancing the distribution of lipophilic drugs and reducing their plasma concentration [10]; (iv) reductions in plasma protein concentration altering drug-free fraction [11]; (v) variation in CYP isozyme expression altering clearance and half-life [12–14]; and (vi) increasing in renal function and glomerular filtration rate altering renal clearance [15].

Venlafaxine is used by approximately 10% of pregnant women during pregnancy [16–18] for the treatment of depression and anxiety disorders. While there is a lack of information on the effects of venlafaxine on the foetus, it is generally accepted that the drug may be used safely throughout pregnancy [16, 19]. The Food and Drug Administration has classified venlafaxine as a 'pregnancy category C' [20]. The benefits of therapy need to be evaluated against the risks of discontinuing treatment and the resulting effects on the mother and child because of the strong correlation between maternal mental health and child development [21].

Venlafaxine is a bicyclic antidepressant that belongs to the serotonin-norepinephrine reuptake inhibitors [22–27]. Venlafaxine therapeutic plasma concentrations have been reported to range from 25 to 400 ng/ml [28, 29], with toxicity commencing at approximately 800 ng/ml [30]. It is mainly metabolised by CYP2D6 and with a minor contribution of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 [31], with a half-life of approximately 5 h [32].

CYP2D6 is a highly polymorphic drug-metabolising enzyme [33] and contributes to the wide interindividual variability in venlafaxine plasma level [22, 34–38]. During pregnancy, CYP2D6 activity increases and hence may lead to a decrease in venlafaxine plasma exposure in comparison with postpartum values [39, 40].

Clinically, reports are sparse confirming changes in maternal venlafaxine plasma concentrations in each trimester.

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A report by Klier *et al.* [41] highlighted the inconsistency in a case report in which venlafaxine's elimination half-life during pregnancy was reduced by a factor of two compared to the post-partum period. However, the AUC in the same patient decreased three times in comparison with the post-partum period [41]. In another study, Ter Horst *et al.* [42] examined seven pregnant women and detected a decrease in plasma concentration of venlafaxine and its metabolite (O-desmethylvenlafaxine) below the therapeutic range in three women during the first trimester, in one woman during the second trimester, and in two women during the third trimester. Furthermore, these findings are also consistent with other studies that revealed a decrease in maternal plasma concentrations for CYP2D6-metabolised antidepressants such as paroxetine, duloxetine, and fluoxetine [40, 43]. More recently, Westin *et al.* [40] indicated a tendency towards a statistically significant decrease in venlafaxine concentrations but no change in metabolite concentrations in a study with 33 pregnancies.

Given the paucity of pharmacokinetic data for venlafaxine during pregnancy, pharmacokinetics-based virtual clinical trials provide an opportunity to pragmatically assess the impact of gestation and CYP2D6 polymorphism on maternal plasma concentrations through gestation [43–46]. The primary value of such models is the integration of gestational age-dependent changes in patient physiology, metabolising enzymes, and drug transporters, together with the capacity to untangle inter-subject variability due to phenotypic or physiological variations [47]. Through the application of such approaches, it is possible to bridge the paucity in pregnancy pharmacokinetic data for venlafexine to better support dose adjustments through gestation and in complex pharmacogenetic phenotypes to support optimal maternal mental health.

The primary aim of this study was to employ the approach of mechanistic pharmacokinetic modelling and virtual clinical trials to assess changes in maternal and foetal venlafaxine plasma venlafaxine concentrations during gestation, and to develop a clinically appropriate dose adjustment approach that could be followed to maintain plasma venlafaxine levels with the therapeutic range throughout gestation, considering the CYP2D6 polymorphic status of subjects.

Methods

The population-based PBPK modelling tool Simcyp® (https://www.certara.com/), was utilized to conduct virtual clinical trials (Simcyp Ltd., a Certara company, Sheffield, UK, Version 20). Simcyp® allows the prediction of drug pharmacokinetics in patient populations and within different subgroups of patients and incorporates physiological, genomic, and demographic data and algorithms accounting for the clinical trial's patients' population variability [48]. A six-stage workflow method was utilised to develop, validate, and simulate phases with venlafaxine (Fig. 1).

Step 1: validation in healthy subjects.

The Simcyp® healthy volunteer (HV) population group was employed to represent 'non-pregnant females' as a baseline, with the Simcyp® 'Pregnancy' population group being used for all gestational investigations. The Pregnancy population group has been used to support pharmacokinetic estimates of plasma concentrations through gestation [43–46, 49], and incorporates necessary gestational-dependent changes in physiology, such as increased blood volume and hepatic enzyme expression, to play a role in modifying drugs' pharmacokinetics [50–52].

To describe venlafaxine within the model, psychochemical and pharmacokinetic parameters describing venlafaxine were collated (Table 1), from a study that previously developed and validated a venlafaxine compound [53] for use in PBPK modelling.

Two single-dose studies and one multiple-dose study utilizing immediate release formulations of venlafaxine were used to validate the model: (i) 30 subjects (22 men and 8 women) received an oral dose of 75 mg while fasting [54]; (ii)

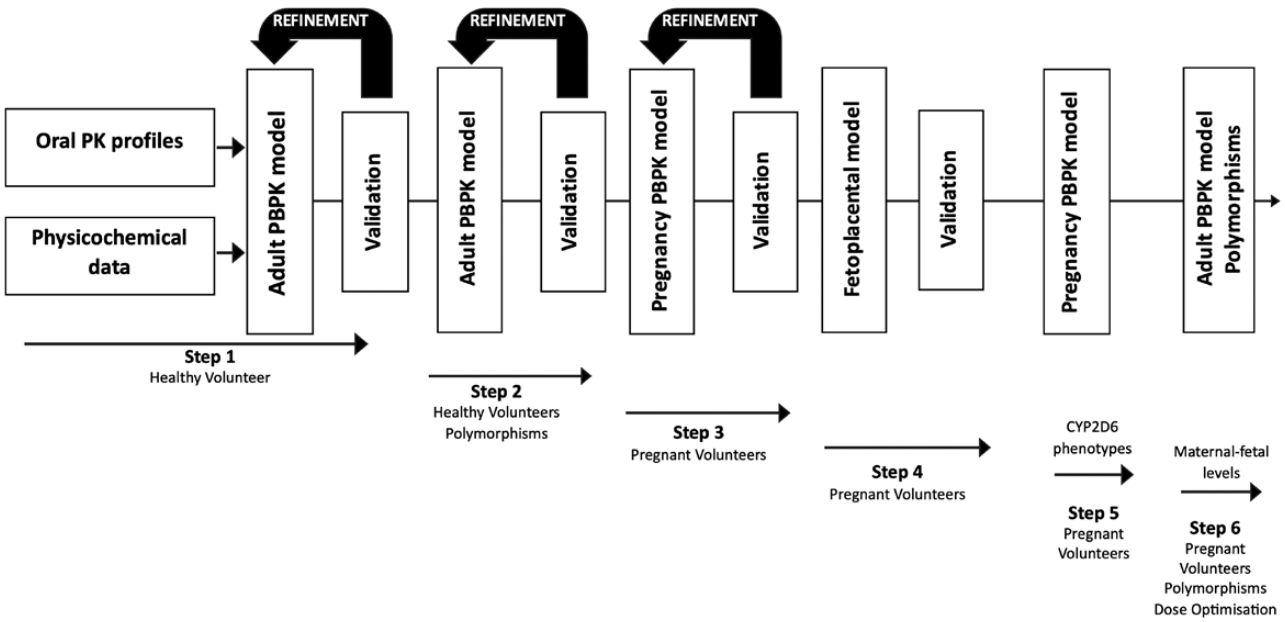

Figure 1. The six-stage workflow model utilized.

Table 1. Parameters for venlafaxine used in PBPK model.

Parameter	Value	Notes
Molecular weight (g/mol)	277.402	
Log P	2.8	
pK_a	9.4	
B/P	1.17	
fu_p	0.73	
fa	0.92	
K_a (h^{-1})	1.31	
T_{lag} (h)	1.44	
K_p scalar	2.37	
V_{ss} (l/kg)	7	Predicted
Enzyme CYP2D6 CLint (µl/min/pmol of isoform)	5.825	
Transplacental diffusion:		
Maternal placenta barrier (CL_{PDM}) and the placental foetal barrier (CL_{PDF})	0.466	Predicted (See step 2.4)

Unless otherwise stated, all data were obtained from previously publish model [53]. Log P, partition coefficient; pK_a, acid dissociation constant; B/P, blood:plasma ratio; fu_p, unbound fraction in plasma; fa, fraction of dose absorbed; K_a, absorption rate constant; T_{lag}, absorption time lag; K_p scalar, partition coefficient scalar; V_{ss}, volume of distribution at steady state; Cl_{int}, intrinsic clearance.

46 subjects aged 18–45 received an oral dose of 75 mg [55]; (iii) 12 men and 12 women aged 18–45 years administered a 75 mg oral dose for 4 days [56].

Furthermore, we extended the validation to incorporate clinical studies utilizing extended-release formulations. We used a previously published modified-release dissolution profile [57] for venlafaxine ER capsule 75 mg and osmotic pump tablets to appropriate model the dissolution and absorption profile (see supplementary Fig.S1). For validation, two single dose and one multiple oral dose studies were used to validate the extended-release venlafaxine model: (i) 30 subjects received a single 75 mg oral dose of venlafaxine extended-release osmotic pump tablets and an extended-release capsule of a single oral dose of 75 mg venlafaxine were administered to 30 HV subjects USFDA [58]. Moreover, twice-daily doses were examined for pharmacokinetic changes in 18 subjects who were given an oral dose of 75 mg venlafaxine every 12 h for 4 days [59].

Step 2: validation in CYP2D6 phenotyped subjects

Given the role of CYP2D6 as the major metabolism pathway for venlafaxine, we subsequently validated the model using reported studies describing venlafaxine pharmacokinetics in phenotyped subjects: (i) a single 75 mg oral dose administered to 14 HVs (20–51 years) with 7 poor metaboliser (PM) and 7 (extensive metaboliser) EM phenotypes and sampling for 4 days [34]; (ii) a single 75 mg oral dose administered to 14 HVs (18–44 years) with 7 PM and 7 EM phenotypes and sampling for 4 days [35].

Simulations were conducted using a 10 × 10 trial design (10 subjects per trial centre and a total of 10 trial centres = 100 subjects) in HV subjects using a similar dosing strategy. To examine polymorph-specific population, the CYP2D6 EM or PM frequency was adjusted to 1 to reflect entirely EM or entirely PM population groups. In addition, the intrinsic clearance (CLint) was adjusted for the PM to 0.088 (µl/min/pmol), and 1.2 (µl/min/pmol) for EM phenotypes, based upon the published *in vitro* clearance data of both phenotypes [60].

Step 3: validation in pregnancy

Venlafaxine plasma concentrations have been investigated during gestation from a retrospective analysis of therapeutic drug monitoring services in Norway, including of 36 plasma drug concentrations during pregnancy and 44 drug concentrations at baseline (non-pregnancy females) obtained from 33 women taking an oral dose of 100 mg daily [40].

The pregnancy population group was used to simulate plasma concentrations in a 10 × 10 trial design (100 subjects) with a 100 mg daily oral dose throughout gestation. Data were collected over the final 24 h of every fifth week starting from week 1 until week 39 of gestation. The trial design was also replicated for HV population of non-pregnant females (baseline) dosed under the same dosing strategy for comparison.

Step 4: validation of foetal cord concentrations

Previous studies reported that venlafaxine can cross the placenta and may be associated with reported postnatal adaptation syndrome in newborns [61–63]. The pregnancy model incorporates a fetoplacental sub-model, which models the placental transfer of drugs into the foetal blood and tissue. Therefore, we applied fetoplacental model to evaluate foetal exposure level during pregnancy. This model incorporates compartments accounting for foetal blood, foetal body tissues, and a description of transplacental clearance, the latter of which is calculated using a permeability-limited model. The model described the compound flux between the maternal, placental, and foetal clearance values with respect to the maternal-placental Cotyledon clearance values (CL_{PDM} and CL_{PDF}). Given the lack of reported venlafaxine transplacental permeability, we utilized an *in vitro–in vivo* extrapolation method that utilizes the hydrogen bond donors (HBD), polar surface area (PSA), and correction for placental villous surface area to yield both CL_{PDM} and CL_{PDF} [64], which utilizes HBD, PSA, and correction for placental villous surface area to yield both CL_{PDM} and CL_{PDF} [46] (Table 1). The placental villous surface area was derived from a meta-analysis of reported values and calculated using Equation (1) as follows and incorporated into the pregnancy model [46]:

$$\text{placental villous surface area } (m^2) = (0.135 \times GW) - (0.023 \times GW^2) + (0.0015 \times GW^3) - (0.00002 \times GW^4). \quad (1)$$

To validate the foeto-placental model, we used three previously published clinical data sets to evaluate the umbilical cord concentration of venlafaxine in different multiple oral doses: (i) nine pregnant women (28–40 years) were administered multiple oral doses of venlafaxine as follows 37.5mg (two subjects), 75 mg (three subjects), 112.5 mg (one subject), 150 mg (two subjects), and 225 mg (one subject) [65]; (ii) 150 mg every 12 h daily was given to three pregnant women with subsequent umbilical cord concentration reported in twins [66]; (iii) 75 mg daily administered to two women during gestation [67].

Given the low subject numbers in the reported studies, we utilized a standard 10 × 10 trial design (100 subjects) aged 20–50 years with sampling of umbilical cord concentrations over the final 7 days of pregnancy to term [65–67].

Step 5: the impact of CYP2D6 polymorphism on venlafaxine plasma concentration during pregnancy

In order to assess the impact of CYP2D6 polymorphisms on venlafaxine plasma concentrations in ultrarapid metabolisers (UM), EM and PM phenotypes during gestation, simulations were conducted utilizing a 10 × 10 trial design for each phenotype, with subjects administered 75 mg one daily dose throughout gestation, with a sampling of plasma concentrations over a 7 days period every fifth week of gestation. Furthermore, the percentage of subjects with trough plasma concentrations below the therapeutic range (25–400 ng/ml) was recorded [28, 29].

Step 6: dose optimization of venlafaxine and foetal exposure during pregnancy in CYP2D6 phenotyped subjects

In order to assess the requirement for dose optimization through gestation, the impact dose escalation on maternal and foetal cord plasma concentrations was examined. Doses were escalated in increments of 37.5 mg to a maximum daily dose of 375 mg, with the therapeutic range considered as 25–400 ng/ml [28, 29], given in divided (12 h) dose. Predicted plasma concentrations were collected for UM, EM, and PM phenotypes in week 6 (mid-Trimester 1), week 18 (mid-Trimester 2), and week 40 (term). The percentage of subjects with trough plasma concentrations <25 ng/ml and >400 ng/ml (therapeutic range), and with peak plasma concentration >400 ng/ml and >800 ng/ml (toxicity range) were reported for each trimester and phenotype [29, 30].

For foetal cord concentration, the Simcyp foeto-placental model can only be utilized from week 15 onward. Cord levels were, therefore, examined at week 18 (mid-Trimester 2), week 30, and week 40 (term) for EM, PM, and UM phenotypes.

Step 7: predictive performance and data analysis

Predictive performance was confirmed through comparison of predicted and reported pharmacokinetic parameters and ensuring these were within 2-fold (0.5–2-fold) [43, 68, 69]. Furthermore, a visual predictive checking strategy was employed for Steps 1–4, which visually compared predicted plasma concentration-time profiles were compared against the observed data. A successful validation approach was assumed when the published profile overlapped and fell within the 5th and 95th percentiles of the predicted median concentration–time profile. Data from published clinical studies was obtained using WebPlotDigitizer v.3.10 (http://arohatgi.info/WebPlotDigitizer/).

For Steps 1, 2 and 4, statistical analysis was conducted using a parametric, unpaired Student's *t*-test to compare the observed and predicted data. In steps 3, 5, and 6, a non-parametric one-way ANOVA with a Dunnett's multiple comparisons post hoc compared every fifth week simulated plasma concentration with the baseline (non-pregnancy) and week 18 for umbilical cord simulation. When comparing phenotype simulated plasma concentration in maternal and umbilical cord concentration, a nonparametric one-way ANOVA with a Tukey's multiple comparisons post hoc test was utilised. A statistical analysis was run using GraphPad Prism Version 8 for Windows (GraphPad Software, La Jolla, CA, USA).

Results

Step 1: validation in healthy subjects

The venlafaxine model was validated using single- and multiple-dose clinical studies (Table 2). The model predicted parameters, including C_{max}, T_{max}, and AUC were within 0.5–2-fold of the reported clinical data. In addition, reported clinical plasma concentration profiles were within the 5th and 95th percentiles of the predicted plasma concentration (Fig. 2). This confirmed successful model validation in the healthy population group.

Table 2. Summary of validation in healthy subjects.

Dose	Study	PK parameters	Observed	Predicted	Prediction Ratio
Single	Wright *et al.* (2009) IR [54]	C_{max}	43.54 (113.07–126.10)	45.31 (51.14–57.67)	1.04
		AUC	649.48 (111.11–124.57)	883.48 (828.50-942.11)	1.36
	Filho *et al.* (2010) IR [55]	C_{max}	34.47 ± 20.4	57.76 ± 20.01	1.67
		AUC	508.50 ± 439.46	946.79 ± 341.08	1.8
		T_{max}	5.89 ± 1.65	7.36 ± 1.27	1.2
	USFDA (2008) ER capsule	C_{max}	50.29	61.33 ± 21.55	1.2
		AUC	802.24	971.6 ± 354.56	1.2
	USFDA (2008) ER osmotic tablet	C_{max}	46.62	61.33 ± 21.55	1.3
		AUC	798.46	971.6 ± 354.56	1.2
Multiple	Troy *et al.* (1995) [59]	C_{max}	189 ± 54	116.28 ± 57.81	0.6
		C_{min}	56 ± 31	86.25 ± 48.53	1.5
		AUC	2677 ± 1031	1272.17 ± 651.79	0.47
	Troy *et al.* (1997) [56]	C_{max}	75 ± 52	87.24 ± 38.06	1.16
		T_{max}	7.2 ± 2.2	6.11 ± 0.77	0.84
		AUC	1220 ± 1039	1583.98 ± 774.95	1.29

AUC, area-under-the-curve to the last time point; C_{max}, maximum plasma concentration; T_{max}, time at maximum plasma concentration. Data represent arithmetic mean (standard deviation) or geometric mean (90% confidence interval) .
AUC: ng/ml h; C_{max}: ng/ml; and T_{max}: h.

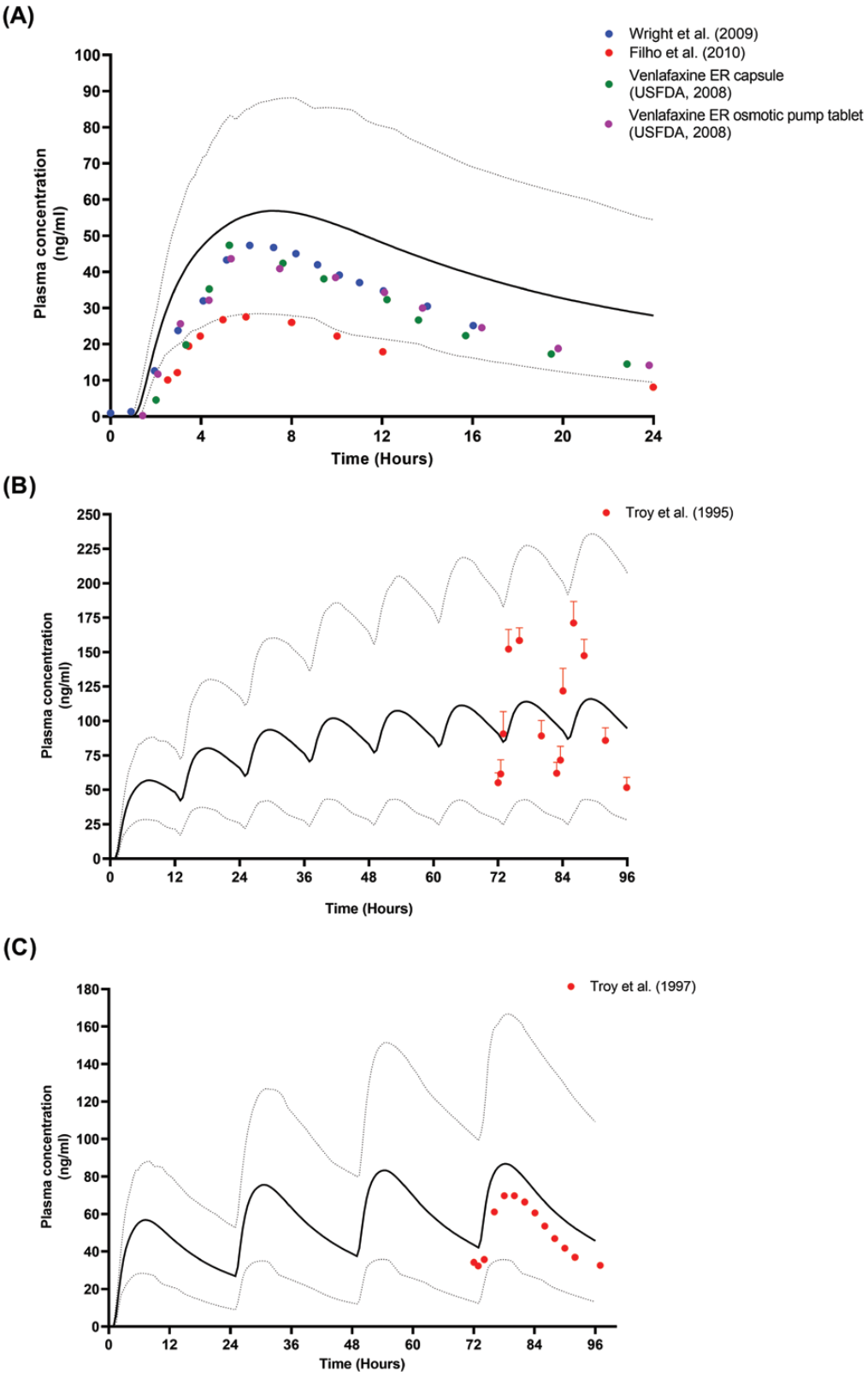

Figure 2. Simulated venlafaxine plasma concentrations following single and multiple dosing in HVs. (a) Single oral 75 mg doses [54, 55, 70]; (b) Multiple oral 75 mg doses twice daily [59]; (c) Multiple oral 75 mg [56]. Solid lines represent the mean predicted concentration-time profile, with dotted lines representing the 5th and 95th percentile ranges. Solid circles represent observed data with error bars represent standard deviation.

Step 2: validation in CYP2D6 phenotyped subjects

To verify the performance of the models in different CYP2D6 phenotyped populations, simulated concentration–time profiles for venlafaxine in the two CYP2D6 phonotypes (EM and PM) were compared with those observed in clinical studies. The model predicted parameters, including C_{max},

T_{max}, and AUC, were within 0.5 to 2-fold of the reported clinical data (Table 3). In addition, reported clinical plasma concentration profiles were within the 5th and 95th percentiles of the predicted plasma concentration. This confirmed successful model validation in CYP2D6 EM and PM phenotype populations (Fig. 3).

Step 3: validation in pregnancy

The verify the predictive performance of the model during pregnancy, model predictions were compared to a published study reported trough plasma concentration through gestation [40]. Reported clinical plasma concentration data broadly overlapped with model predictions every fifth week through gestation (Fig. 4). In addition, the observed mean trough plasma concentration at baseline, 60.18 ng/ml ± 38.44 ng/ml, was similar to trimester 1 (week 5: 60.8 ng/ml ± 40.37 ng/ml), while decreased in trimester 2 (week 20: 50.47 ng/ml ± 37.54 ng/ml) and trimester 3 (week 30: 43.58 ng/ml ± 35.36 ng/ml), with a significant decrease statistically from week 20 onwards to week 40 ($P < 0.05$) (Table 4).

Step 4: validation of foetal cord concentrations

Given the potential for venlafaxine to cross the placenta, the performance of the model of prediction venlafaxine cord concentrations was assessed by compared to studies examined maternal dosages ranging from 37.4 mg to 300 mg per day [65–67]. For venlafaxine, model-predicted median cord plasma concentrations were within the observed range reported in studies across all dose ranges (Fig. 5).

Although only a few individual data points have been reported across three published studies, considerable variability is detected in the cord exposure level. However, according to Paulzen *et al.* [65], the concentration of the drug in the cord was 19 (ng/ml) when the maternal dosage was 75 mg. This value is comparable with the predicted median cord concentration of 18.9 (ng/ml) (supplementary Table S1).

Step 5: the impact of CYP2D6 polymorphism on venlafaxine plasma concentration during pregnancy

The model was subsequently utilized to evaluate the impact of CYP2D6 phenotypes on a standard dose of venlafaxine 75 mg oral dose exposure during pregnancy. Significant decreases in AUC were observed in UM and EM subjects from gestational week 20 onwards when compared to the baseline subjects ($P < 0.01$) (Table 5). For CL, significant increases were evident for UM and EM subjects from week 25 onwards ($P < 0.01$, one way ANOVA) (Table 5). However, no significant changes in venlafaxine pharmacokinetics during gestation were detected for PM subjects (Table 5).

In both EM and UM phenotypes, there was a gradual decrease in venlafaxine peak and trough plasma concentrations with increasing gestational weeks. The percentage of subjects with trough plasma concentrations below the lower limit of the therapeutic window (25 ng/ml) for each phenotype was estimated to identify whether venlafaxine 75 mg as a standard dose required a dose adjustment pregnancy [29]. For both EM and UM populations, approximately 70%–92% of subjects had trough venlafaxine plasma concentrations below the therapeutic range (<25 ng/ml), with the number increasing up to 98% of subjects below the therapeutic range by week 30 (Table 5).

Step 6: dose optimization of venlafaxine and foetal exposure during pregnancy in CYP2D6 phenotyped subjects

Given the impact of CYP2D6 polymorphic state on venlafaxine plasma concentrations, the requirement for dose adjustment through gestation was assessed. The optimal dose was determined when no more than 20% of subjects possessed plasma concentration <25 ng/ml and <400 ng/ml and <800 ng/ml [29, 30].

Table 3. Summary of validation in CYP2D6 phenotyped subjects.

Study	Polymorphsim	PK parameters	Observed	Predicted	Prediction ratio
Preskorn *et al.* (2009) [35]	EM	C_{max}	39.6 ± 14.1	45.63 ± 19.37	1.15
		T_{max}	6.0 (6.0-10.0)	6.39 (3.95–9.40)	1.06
		AUC	591 ± 246	1046.43 ± 610.62	1.77
		Cl/F	139 ± 78	98.13 ± 60.72	0.7
	PM	C_{max}	98.6 ± 10.6	79.42 ± 22.78	0.8
		T_{max}	7.0 (6.0-10.0)	7.94 (5.7–11.4)	1.1
		AUC	2548 ± 451	2703.80 ± 1014.59	1.06
		Cl/F	24 ± 8.4	33.42 ± 11.27	1.3
Nichols *et al.* (2011) [34]	EM	C_{max}	30 ± 17.7	45.63 ± 19.37	1.5
		T_{max}	6	6.39 ± 0.94	1.06
		AUC	518 ± 462	906.43 ± 610.62	1.74
		Cl/F	219.9 ± 124.8	98.13 ± 60.72	0.44
	PM	C_{max}	79.8 ± 32.4	76.42 ± 22.78	0.9
		T_{max}	8	7.94 ± 1.13	0.9
		AUC	3054 ± 3460	2855.89 ± 1125.84	0.9
		Cl/F	35.88 ± 15.6	30.80 ± 12.95	0.8

AUC, area-under-the-curve to the last time point; C_{max}, maximum plasma concentration; T_{max}, time at maximum plasma concentration.; CL/F, oral clearance. Data represent arithmetic mean ± standard deviation or mean (range).
AUC: ng/ml h; C_{max}: ng/ml; T_{max}: h; CL/F: l/h.

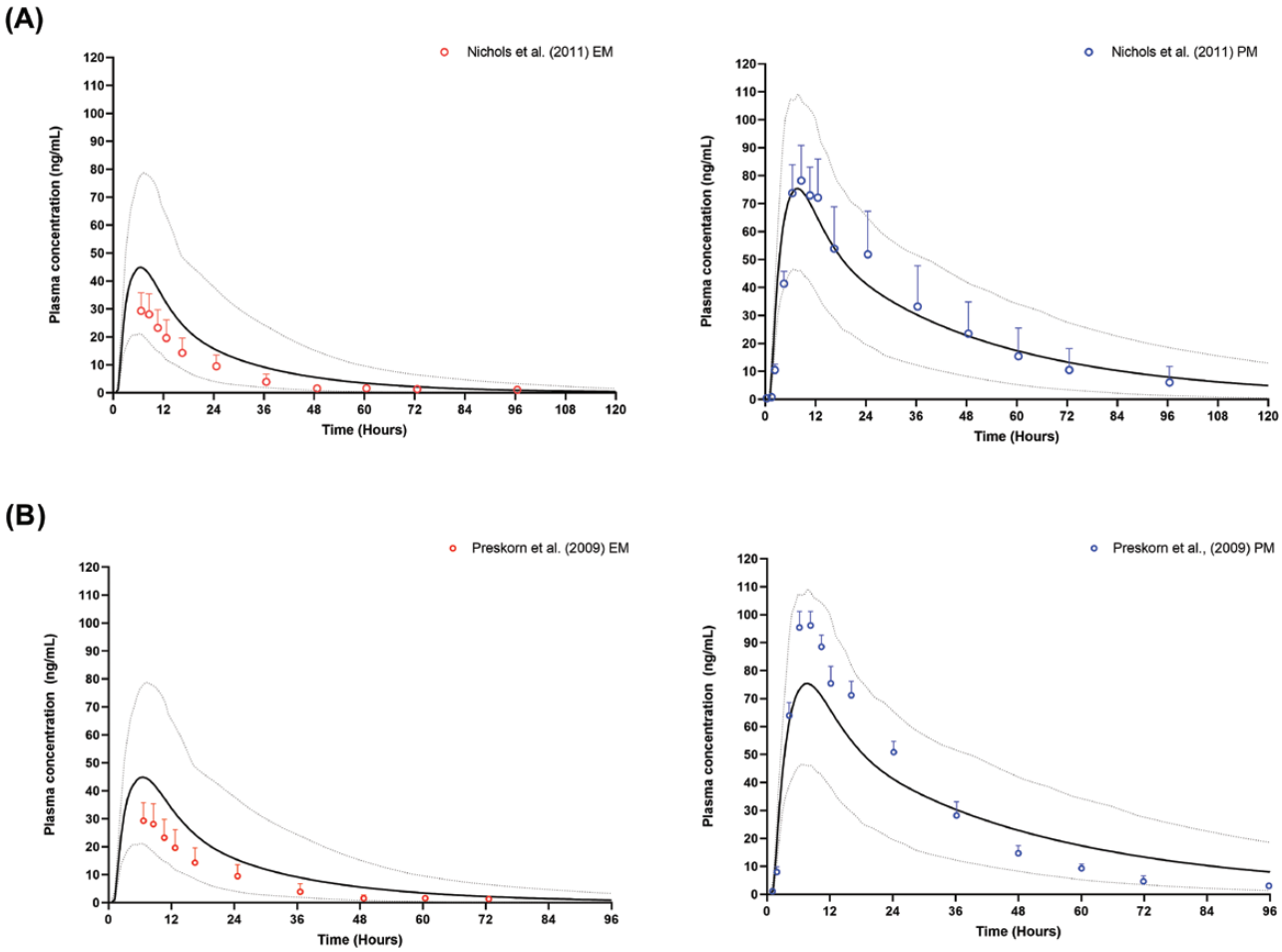

Figure 3. Simulated venlafaxine plasma concentrations following single oral dose 75 mg in CYP2D6 phenotyped populations. Single oral 75 mg doses were administered to: (a) Extensive metaboliser (EM) [left] and poor metaboliser (PM) [right] subjects based on a study by Nichols *et al.* [34]; (b) EM [left] and PM [right] subjects based on a study by Preston *et al.* [35]. Solid lines represent the mean predicted concentration-time profile, with dotted lines representing the 5th and 95th percentile ranges. Solid circles represent observed data with error bars represent standard deviation.

For EM a dose of 225 mg daily in T1 followed by 262.5 mg daily in T2 and increased to 375 mg in T3 is suggested to be optimal. For UM, a dose of 375 mg daily throughout gestation is suggested to be optimal. For PM, a daily dose within the range of 37.5–112.5 mg, throughout gestation, is suggested to be optimal (Fig. 6).

As venlafaxine can cross the placenta, the impact on maternal doses on foetal cord concentrations was also assessed. Regardless of the polymorphic state of CYP2D6, gestation resulted in a significant increase in venlafaxine cord concentration ($P < 0.05$, one way ANOVA) (Fig. 7). At the optimal dose suggested, for EM mother at term (W40), the peak and trough cord concentrations were reduced by 32% and 41.8%, respectively, compared to T2 (W18) ($P < 0.05$). For UM at term (W40), peak cord concentrations were reduced by 36.3%, and trough cord concentrations were reduced by 43.5% ($P < 0.05$) (Fig. 7). However, for PM phenotypes, no statistically significant differences throughout gestation were reported (see supplementary Table S2).

Discussion

Depression is the most frequent psychiatric disorder that affects pregnant women globally It is estimated that 15%–20% of women may suffer from depression at some point in their lives, especially during pregnancy and after delivery [71, 72].

Pregnant women receiving venlafaxine are at risk for subtherapeutic doses due to physiological changes during pregnancy [41, 42]. This study utilized, for the first time, the principle of pharmacokinetic modelling to evaluate the use of venlafaxine in pregnant population groups and aimed to link changes in plasma concentrations during gestation to therapeutic levels for the first time.

Validation in healthy subjects

We adapted a previously published venlafaxine model [53] to enable its use in exploring venlafaxine exposure during gestation; the model was then fully validated with single- and multiple-dose studies in pregnant and nonpregnant subjects. Steps 1 and 2 utilized single and multiple-dose studies in non-pregnant subjects to verify the venlafaxine model (Step 1) (Table 1) and to assess the ability to recapitulate the impact of CYP2D6 polymorphisms on pharmacokinetic (Step 2) (Table 2). In all cases, validation was successful and pharmacokinetic parameters were within a 2-fold range of the observed venlafaxine pharmacokinetics parameters.

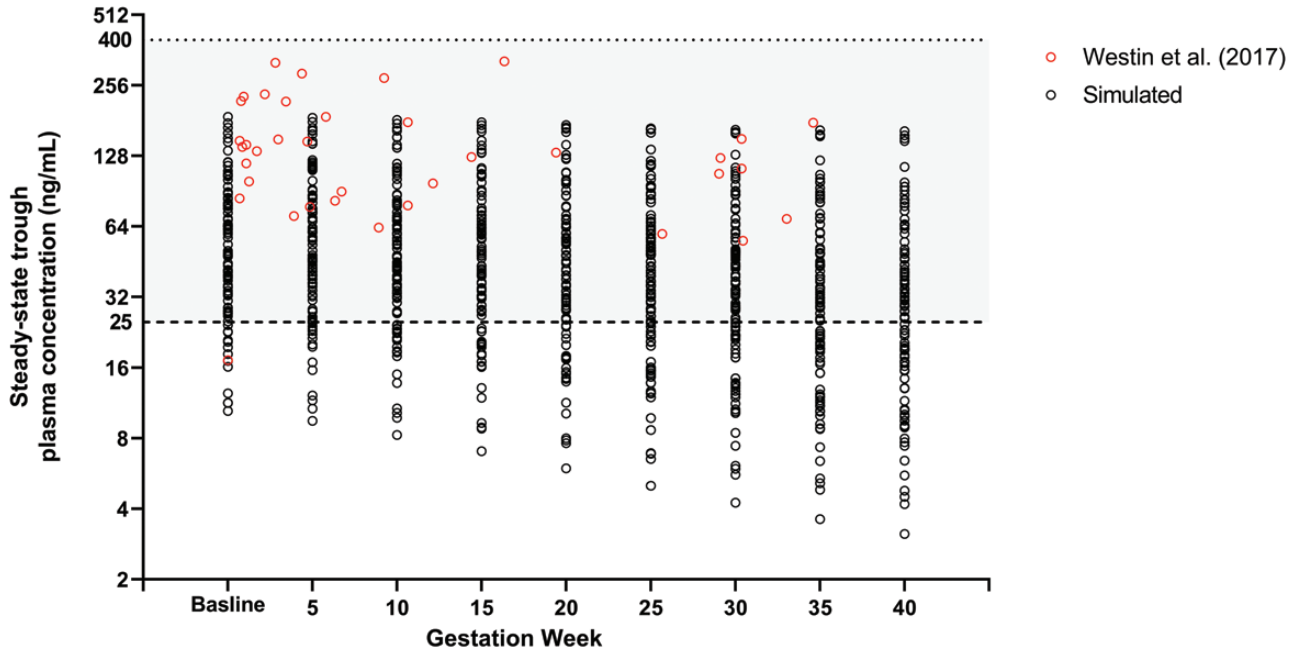

Figure 4. Simulated venlafaxine plasma concentrations throughout pregnancy. Simulated trough plasma concentrations collected at 5-week intervals (black open circles) for 100 individuals following a 100 mg daily dose. Non-pregnant women are referred to as 'baseline'. Red open circles reflect observed (pooled) plasma concentrations collected from a total of 33 participants. The therapeutic range is illustrated by the shaded regions between 25 and 400 ng/ml.

Table 4. Summary of pharmacokinetics parameters during pregnancy.

Week	AUC (ng/ml h)	Clearance (l/h)	C_{max} (ng/ml)	C_{min} (ng/ml)	T_{max} (h)	Trough concentration <25 ng/ml (% subjects)
Baseline	2184 ± 1133	60.2 ± 34.7	119.6 ± 54.9	60 ± 38.4	6 ± 0.73	14
5	2275.8 ± 1183.7	57.3 ± 32	126.7 ± 57	60.80 ± 40.3	6.2 ± 0.68	19
10	2172.4 ± 1165	61 ± 35.4	121.5 ± 56.2	57.5 ± 39.5	6.2 ± 0.7	21
15	1986.8 ± 1170	69.9 ± 45.8	115.3 ± 57.8	49.9 ± 38.9	6 ± 0.6	27
20	1850 ± 1149	77 ± 52.3	108.3 ± 57	45.7 ± 38	6 ± 0.6	33
25	1613.6 ± 1128	85.6 ± 60	101.2 ± 56	41.7 ± 37	5.9 ± 0.7	39
30	1582 ± 1106	95.9 ± 0.7	94.2 ± 55.2	37.9 ± 36	5.9 ± 0.7	46
35	1457.9 ± 1085	107.7 ± 80.6	87.5 ± 54.3	34.3 ± 35.3	5.8 ± 0.7	48
40	1342.4 ± 1003.7	121.3 ± 93.2	81.3 ± 53.4	31 ± 34.4	5.7 ± 0.7	55

AUC, area-under-the-curve to the last time point; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; T_{max}, time at maximum plasma concentration.; CL, oral clearance. Data represent arithmetic mean ± standard deviation.

Validation in pregnancy

There are presently inadequate pharmacokinetic data evaluating the influence of gestation on plasma venlafaxine concentrations. In this study, the venlafaxine pregnancy PBPK model was validated based on a study by Westin *et al.*, who reported venlafaxine plasma concentrations collected in patients during gestation [40]. Simulations were run for the whole gestational period (40 weeks), and sampling and quantification were performed on the last day of every fifth week of pregnancy (Weeks 0–40) (Fig. 4). In non-pregnant subjects ('baseline'), the simulated mean trough plasma concentrations (60.18 ng/ml ± 38.44 ng/ml) were within 2-fold of those reported (35.5 ng/ml) (Table 4) and covered an additional virtually identical range of reported values (Fig. 4). Westin reported a statistically significant decline in venlafaxine concentrations during gestation [40], with a similar decrease observed in our studies from week 20 onwards to week 40 ($P < 0.05$) (Fig. 4). The decrease in venlafaxine plasma concentration is likely a result of the increased CYP2D6 expression throughout gestation [15, 52, 73], which reflects the increase in venlafaxine predicted clearance during gestation (Table 4). This trend has been recapitulated in other pharmacokinetic modelling studies for several compounds, namely, metoprolol and paroxetine [43, 74]. Furthermore, given that venlafaxine is a lipophilic drug, the expansion of intravascular and extravascular volume and increase in body fat throughout the gestational period [75, 76], is likely to further contribute to this decrease in venlafaxine plasma concentrations through gestation (Table 4).

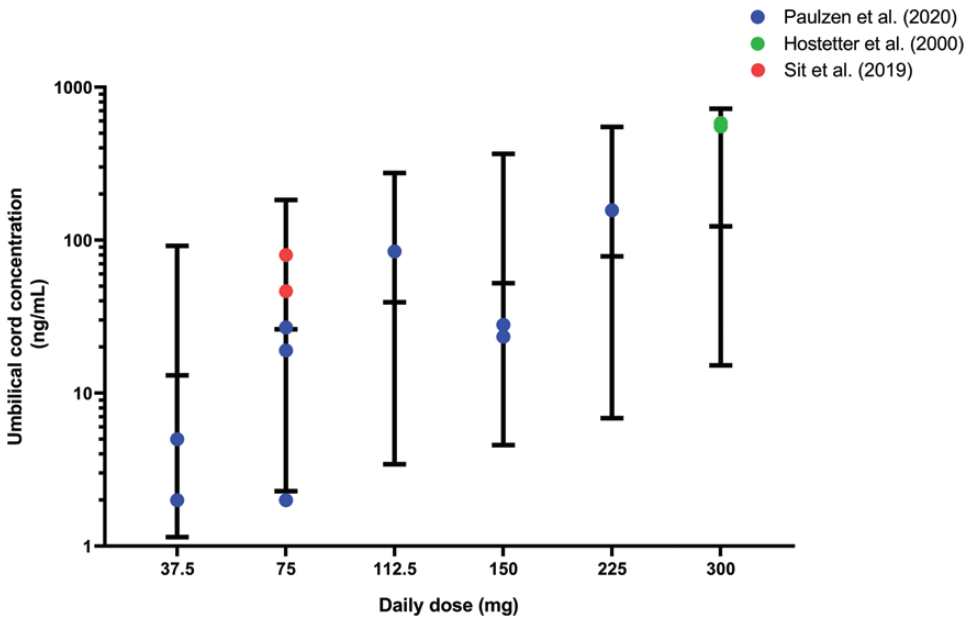

Figure 5. Simulated venlafaxine umbilical cord concentrations at term. Solid vertical lines represent predicted (trough) range, medium and maximum and minimum predicted value. Coloured open circles indicated reported umbilical cord concentrations in individual subjects.

Validation of foetal cord concentrations

There is currently a paucity of studies investigating foetal venlafaxine exposure. To our knowledge, only three publications (to date) containing foetal umbilical cord concentrations were sampled in the foetus after delivery [65–67]. Thus, we applied the feto-placental model to predict venlafaxine foetal cord concentrations using physicochemical properties of venlafaxine placental permeability. The resulting observed individual data fell within the median and range of simulated venlafaxine foetal concentration for each dose (37.5–300 mg) (Fig. 5). Higher variability was detected with observed venlafaxine foetal data, possibly due to varying time between drug administration and sample collection [77, 78], and it is also unknown if the cord level was at the peak or the trough plasma concentration. Despite the limited data on venlafaxine cord concentration observed data, the model captured most of the reported concentration, thus, validated the fetoplacental model (Supplementary Table S1).

The impact of CYP2D6 polymorphism on venlafaxine plasma concentrations during pregnancy

There is currently a lack of pharmacokinetics data examining the impact of CYP2D6 phenotypes on venlafaxine plasma concentrations during gestation Therefore, to investigate a correlation in the decrease in venlafaxine plasma levels during gestation and CYP2D6 phenotype, we further assessed changes in total clearance and AUC. This was determined for each subject's CYP2D6 phenotype. The clearance increased in the EM and UM phenotypes throughout pregnancy, reflecting the increase in CYP2D6 activity observed during pregnancy [52, 79, 80], with the largest difference in clearance occurring in week 25 gestation (Table 5). For PM phenotypes, the increase in CYP2D6 activity during gestation does not influence venlafaxine clearance since the PM phenotype inherited two inactive alleles which lost CYP2D6 enzyme activity [22, 37, 81].

Tracy *et al.* reported an increase in CYP2D6 activity of 25% between 14 and 18 weeks of gestation, 35% between 24 and 28 weeks, and 50% between 36 and 40 weeks of gestation compared with postpartum [39]. CYP2D6 activity has increased because of increasing the essential female hormone's oestradiol and progesterone levels during pregnancy [82]. As a result, our finding demonstrated that a decrease in plasma concentrations may be associated with temporal changes and increases in CYP2D6 expression noted throughout gestation. This induction during gestation demonstrated a highly significant influence on UM and EM phenotype subjects in decreasing peak (C_{max}) and trough (C_{min}) (Table 5).

Dose optimization of venlafaxine and foetal exposure during pregnancy in CYP2D6 phenotyed subjects.

Venlafaxine dose optimisation in phenotyped subjects

To determine the influence of these polymorphic patients on potentially subtherapeutic levels, we calculated the proportion of participants having trough concentrations below the lower therapeutic window (25 ng/ml) every 5 weeks, with all subjects receiving a standard oral dosage of 75 mg daily. From week 15 of gestation, >85%–79% of the UM and EM phenotypes demonstrated trough plasma concentration below therapeutic range (25–400 ng/ml) (Table 5). While for the PM phenotypes, this remained at 4% from weeks 5–40 (Table 5). Considering this variation, we examined how a dosage adjustment for UM, EM, and PM phenotypes may be made during pregnancy.

The pharmacogenetics working group of the Royal Dutch Pharmacists' Association has analysed the effects of CYP2D6 genotype on venlafaxine dosage recommendations for clinical use. For subjects possessing PM phenotypes, it is suggested that a switch to a medicine that is not metabolized by this enzyme or lowering the dosage is required. Whereas for UM phenotypes, an increase in dose to 150% of the usual dose is suggested [83]. For all phenotypes studied, the standard 75

Table 5. Summary of pharmacokinetics parameters in CYP2D6 polymorph subjects during pregnancy.

Week	AUC (ng/ml h)	CL (l/h)	C_{max} (ng/ml)	C_{min} (ng/ml)	T_{max} (h)	Trough concentration <25 ng/ml (% subjects)
EM phenotype						
Baseline	947.8 ± 569	108.4 ± 65.5	58.7 ± 30.6	21.5 ± 17.1	5.5 ± 0.7	70
5	966.5 ± 566	106.6 ± 66.7	60.8 ± 30.6	20.9 ± 16.8	5.7 ± 0.7	70
10	886.9 ± 531	117.6 ± 79.9	56.3 ± 29	18.7 ± 15.6	5.7 ± 0.7	74
15	801.1 ± 493.7	131.9 ± 85.8	51.2 ± 27.2	16.6 ± 14.2	5.7 ± 0.7	79
20	715.4 ± 453.4	149.8 ± 99.3	45.8 ± 25.1	14.9 ± 12.8	5.7 ± 0.7	86
25	634.2 ± 413.1	171.4 ± 115.7	40.7 ± 23	12.7 ± 11.5	5.7 ± 0.7	91
30	559.7 ± 374.3	180.7 ± 115.8	35.9 ± 21	11.1 ± 10.3	5.7 ± 0.7	92
35	492.9 ± 337.8	226.2 ± 157.5	31.6 ± 19.1	9.6 ± 9.1	5.6 ± 0.7	92
40	433.7 ± 304.1	259.9 ± 183.3	28 ± 17.4	8.4 ± 8.1	5.5 ± 0.7	98
UM phenotype						
Baseline	615 ± 415.6	178.6 ± 118.5	50.9 ± 24.1	12.1 ± 11.3	5.2 ± 0.7	90
5	618.2 ± 408.8	177.1 ± 120.7	40.9 ± 24	11.4 ± 10.8	5.3 ± 0.7	92
10	558.5 ± 377.4	198.1 ± 136.8	38.2 ± 22.4	10 ± 9.7	5.3 ± 0.7	92
15	496 ± 343	225.7 ± 157.9	34.1 ± 20.6	8.7 ± 8.6	5.4 ± 0.7	95
20	435.5 ± 308.2	260.1 ± 184.2	30 ± 18.7	7.5 ± 7.6	5.4 ± 0.7	97
25	379.8 ± 274.9	301.5 ± 216	26.2 ± 16.8	6.4 ± 6.6	5.5 ± 0.6	98
30	330.2 ± 243.9	350.3 ± 253.5	22.7 ± 15	5.5 ± 5.7	5.5 ± 0.6	98
35	286.8 ± 215.8	406.9 ± 297	19.7 ± 13.3	4.8 ± 5	5.4 ± 0.6	98
40	249.3 ± 190.7	237.2 ± 155.3	17.2 ± 11.9	4.3 ± 4.1	5.2 ± 0.6	99
PM phenotype						
Baseline	2569.7 ± 1062.9	34.6 ± 15.2	132.8 ± 49.8	78 ± 37.5	6.4 ± 0.6	4
5	2883 ± 1216.7	31.2 ± 14.5	150.1 ± 56.2	85.7 ± 43.7	6.7 ± 0.5	4
10	2863.1 ± 1207.6	31.4 ± 14.6	148.7 ± 55.7	85.3 ± 43.2	6.8 ± 0.5	4
15	2837.7 ± 1193.9	31.7 ± 14.7	146.5 ± 54.9	85 ± 43	6.9 ± 0.5	4
20	2807.2 ± 1176.2	32 ± 14.9	143.9 ± 53.9	69.9 ± 45.5	7 ± 0.5	4
25	2772.3 ± 1155.6	32.4 ± 15	140.9 ± 52.8	84.5 ± 41.8	7.1 ± 0.5	4
30	2733.7 ± 1133	32.8 ± 15.1	137.8 ± 51.5	84 ± 41.1	7.1 ± 0.5	4
35	2692.2 ± 1109.4	33.2 ± 15.3	134.7 ± 50.3	83.4 ± 40.3	7.1 ± 0.6	4
40	2648.7 ± 1086	33.7 ± 15.5	132.1 ± 49.2	82.5 ± 39.4	6.9 ± 0.6	4

AUC, area-under-the-curve to the last time point; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; T_{max}, time at maximum plasma concentration.; CL, oral clearance. Data represents arithmetic mean ± standard deviation.

mg daily dose required adjusting throughout gestation, given the reported venlafaxine therapeutic range of 25–400 ng/ml [29] (Fig. 6).

Our results highlight that for EM phenotypes, a daily dosage of 225 mg in the first trimester, followed by 262.5 mg in the second and 375 mg in the third, is suggested to be optimal. For UM phenotypes a 375 mg daily dose throughout gestation is suggested to be optimal. For PM phenotypes, a 37.5–112.5 mg daily dose throughout gestation is suggested to be optimal (Fig. 6). However, venlafaxine and O-desmethylvenlafaxine have equivalent pharmacological characteristics and the total of blood concentrations venlafaxine and O-desmethylvenlafaxine have been reported to be similar in EM and UM [22], while other studies reported that UM phenotypes have a higher ratio of venlafaxine and metabolite [84]. However, an association between treatment resistance and CYP2D6 gene duplication has been reported [85].

In our studies, although we utilized a lower limit of 25 ng/ml, the range of trough concentrations in UM for all trimesters was between 4- and 10-fold lower than this limit (Table 5). In order to recover this decrease in venlafaxine plasma concentration, we identified a dose increase to 375 mg, to be acceptable. This upper dose is within the recommended dosing range for venlafexine, however, given pharmacologically active nature O-desmethylvenlafaxine, further studies are required to assess the relationship between dose and clinical effect in UM metabolisers. Current guidelines from DPWG suggest an increase in dose by 150% of the standard dose and/or switching to a non-CYP2D6 agent [83].

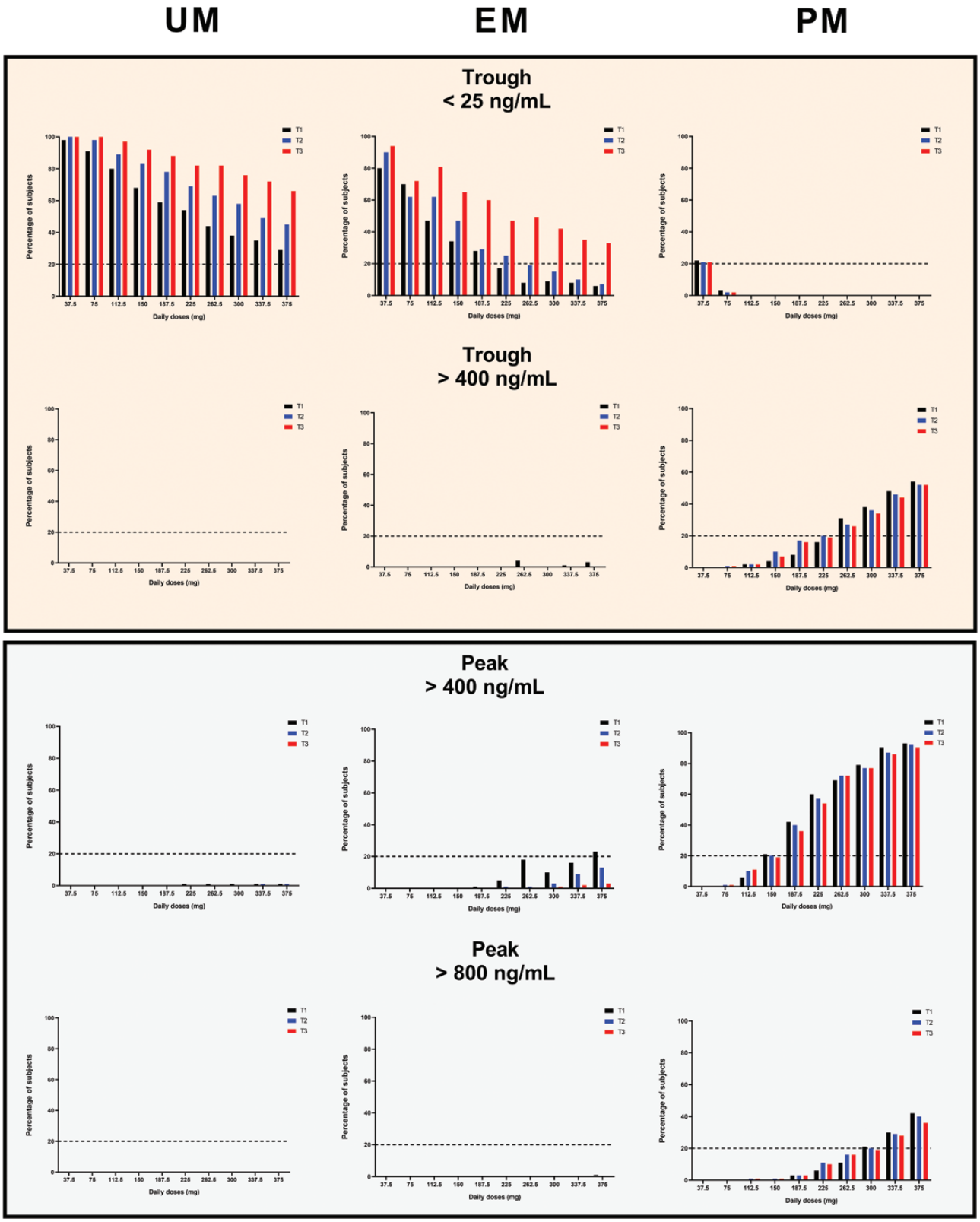

Figure 6. Dose optimization through gestation. Venlafaxine doses were escalated from 37.5 mg to 375 mg once daily, with quantification of subjects with maternal trough and maternal peak concentrations below or above the therapeutic window. These windows were set at trough concentration <25 ng/ml and >400 ng/ml (therapeutic range), and >400 ng/ml and >800 ng/ml (toxicity range). Dashed horizontal lines represent the threshold defined as 20% of subjects.

Foetal exposure during gestation

We further investigated the impact of increasing venlafaxine dose and CYP2D6 polymorphism on foetal exposure for UM, EM, and PM subjects. For UM and EM, foetal exposure was decreased significantly at term (W40) compared to T2 (W18) (Fig. 7) (see supplementary material Table S2), because the

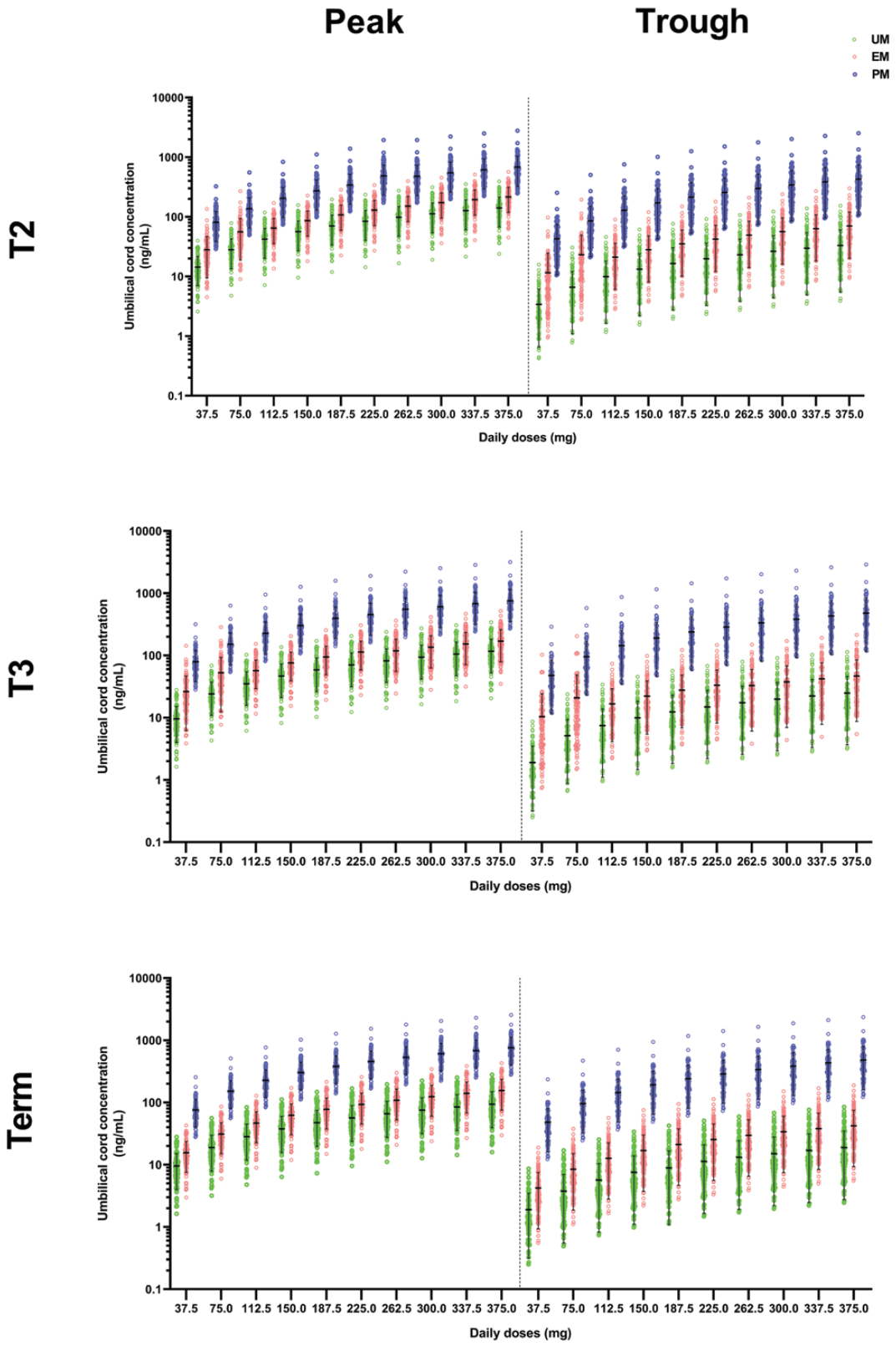

Figure 7. The impact of dose escalation on foetal cord concentrations. Venlafaxine doses were escalated from 37.5 mg to 375 mg once daily, with quantification of foetal cord concentrations (n = 100 subjects) in the middle of the second trimester (T2), third trimester (T3) and at term for UM phenotypes (green circles), EM phenotypes (pink circles) and PM phenotypes (blue circles).

foetal liver contains CYP450 enzymes, including CYP2D6, which participate in decreasing venlafaxine foetal concentration [86]. However, for PM subjects, cord level did not significantly change at term (W40). Unfortunately, to date, there is no clear target for the safety level of foetus exposure to venlafaxine (see supplementary materials Table S2).

Limited and contradictory studies have examined the impact of foetal venlafaxine. The APGAR score is a rapid approach for assessing newborns (appearance, pulse, grimace, activity, and respiration) soon after delivery [87]. In one study examining 9 babies, three had low APGAR scores and required monitoring following foetal venlafaxine exposure of 19–26 ng/ml [65]. However, in the same study, higher concentrations of venlafaxine were detected at the cord level, with no adverse effects detected in the newborns [65]. Moreover, Hostetter *et al.* evaluated venlafaxine cord concentrations in twins who received a 300 mg maternal daily dose, and the cord level for the twin ranged from 554 to 584 ng/ml; the twins were healthy [66].

The range of foetal cord concentration predicted within this report for all polymorphisms spans the ranges highlighted in the aforementioned clinical studies, but it is evident that further clinical studies are required to better understand the implications of exposure on foetal health.

Previous studies demonstrated that there are insignificant differences between maternal venlafaxine level and cord concentration [67, 88]. Considering that, the foetus is continually exposed to the substances by ingestion, transcutaneous absorption, and breathing exposure of amniotic fluid, with the latter bypassing foetal hepatic metabolism and perhaps accounting for the high quantities seen in amniotic fluid [88]. The physiochemical features of the drug have a role in the transfer of compounds through the placenta including the molecular weight of a substance, lipid solubility, and protein binding in maternal and foetal circulation [89, 90].

Conclusion

Venlafaxine plasma concentrations have been shown to decrease during pregnancy to an extent determined by the polymorphism of CYP2D6. This study has demonstrated the application of PBPK to support precision dosing to improve treatment of the depression in pregnancy population groups in the context of phenotyped populations.

For the UM and EM phenotypes, a reduction in trough plasma concentrations was simulated during pregnancy. In contrast to PM phenotypes (4%), a significant portion of ultra-rapid and extended phenotypic patients had trough levels below 25 ng/ml (87–96%). All phenotypes examined required daily adjustments to the standard 75 mg dosage for the duration of pregnancy. For EM phenotypes, 225 mg daily in T1, then 262.5 mg daily in T2, and 375 mg daily in T3 is recommended; for UM phenotypes, 375 mg daily throughout gestation is recommended; and for PM phenotypes, a 37.5–112 mg daily is suggested to be optimal throughout pregnancy.

Future clinical studies should be conducted to verify the recommendations within this study, in addition to assessing the impact of altered exposure on foetal development. Furthermore, given that venlafaxine is metabolized to the active metabolite O-Desmethy venlafaxine (ODV), potential changes in plasma concentrations of ODV should be further studied in pregnant subjects in order to understand the impact of the phenotypes on ODV levels and ots potenital to alter clinical outcomes [42].

Supplementary data

Supplementary data are available at *Journal of Pharmacy and Pharmacology* online.

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Author contributions

All authors contributed equally to the article.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical statement

None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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