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The application of precision dosing in the use of sertraline throughout pregnancy for poor and ultra-rapid metaboliser CYP 2C19 subjects: a virtual clinical trial pharmacokinetics study

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Running header

Pharmacokinetics of sertraline during pregnancy

ABSTRACT

Background: Sertraline is known to undergo changes in pharmacokinetics during pregnancy. CYP 2C19 has been implicated in the inter-individual variation in clinical effect associated with sertraline activity. However, knowledge of suitable dose titrations during pregnancy and within CYP 2C19 phenotypes is lacking.

Methods: A pharmacokinetic modelling virtual clinical trials approach was implemented to: (i) assess gestational changes in sertraline trough plasma concentrations for CYP 2C19 phenotypes and (ii) to identify appropriate dose titration strategies to stabilise sertraline levels within a defined therapeutic range throughout gestation.

Key Findings: Sertraline trough plasma concentrations decreased throughout gestation, with maternal volume expansion and reduction in plasma albumin being identified as possible causative reasons. All CYP 2C19 phenotypes required dose increase throughout gestation.

Conclusions: For extensive metaboliser (EM) and ultra-rapid metaboliser (UM) phenotypes, doses of 100-150 mg daily are required throughout gestation. For poor metabolisers (PM), 50 mg daily during trimester 1 followed by a dose of 100 mg daily in trimesters 2 and 3 are required.

KEYWORDS

Sertraline; pharmacokinetics; PBPK; pregnancy; phenotype.

1. INTRODUCTION

Depression throughout pregnancy is known to affect up to 20 % of women (Fisher et al., 2012; Vigod, Wilson, & Howard, 2016), although fewer than 20 % of pregnant women will actually receive suitable treatment (Byatt, Xiao, Dinh, & Waring, 2016; Geier, Hills, Gonzales, Tum, & Finley, 2015). The risk of untreated depression is particularly important given that death associated with suicide can affect 1 in every 25 women aged 20-35 years, from conception through to the post-natal period (J. J. Kim & Silver, 2016). In addition, antenatal depression is a major risk factor for developing postnatal depression (McAllister-Williams et al., 2017). A key strategy in the management of moderate-to-severe depression is the use of selective serotonin reuptake inhibitors (SSRIs) as first-line agents and which include sertraline, citalopram, fluoxetine, paroxetine and fluvoxamine.

Sertraline is one of the most frequently used SSRIs globally, particularly during pregnancy (Bérard, Zhao, & Sheehy, 2017; Colvin, Slack-Smith, Stanley, & Bower, 2011; Nordeng et al., 2012; Oberlander et al., 2008; Ramos, Oraichi, Rey, Blais, & Berard, 2007; Reis & Kallen, 2010; Zakiyah et al., 2018), and is commonly used to manage, amongst others, anxiety and panic disorders and obsessive-compulsive disorders (Pae & Patkar, 2007; Westin, Brekke, Molden, Skogvoll, & Spigset, 2017). Furthermore, SSRIs have been demonstrated to be lead to very few birth defects (Byatt, Deligiannidis, & Freeman, 2013).

Sertraline is metabolised by multiple Cytochrome P450 enzymes, including primarily CYP 2C19 and 2B6 (Saiz-Rodríguez et al., 2018) along with contributions from CYP 2C9, CYP 2D6 and CYP 3A4 (Obach, Cox, & Tremaine, 2005) and is a moderate inhibitor of CYP 2D6 (Alfaro, Lam, Simpson, & Ereshefsky, 2000; Lam, Gaedigk, Ereshefsky, Alfaro, & Simpson, 2002). Confounding the use of sertraline in pregnancy are the longitudinal changes in CYP isozyme expression during gestation, where expression increases for 2B6 (Koh et al., 2012),

2D6 (Stellan Högstedt, Lindberg, Peng, Regårdh, & Rane, 1985; S Högstedt, Lindberg, & Rane, 1983; Wadelius, Darj, Frenne, & Rane, 1997) and 3A4 (Kosel, Beckerman, Hayashi, Homma, & Aweeka, 2003; Prevost, Akl, Whybrew, & Sibai, 1992) and decreases for 2C19 (McGready, Stepniewska, Edstein, et al., 2003; McGready, Stepniewska, Seaton, et al., 2003; Ward et al., 1991).

The implications of such changes during gestation make dose optimisation challenging, and this is confounded by the paucity of the pharmacokinetic studies for sertraline use during pregnancy. In those that have reported plasma concentrations during gestation, conflicting results indicate either an increase in trough plasma levels (Westin et al., 2017) necessitating possible dose reduction, or a decrease in plasma concentrations requiring a possible dose increase (M. P. Freeman et al., 2008; Marlene P. Freeman et al., 2008; Hostetter, Stowe, Strader, McLaughlin, & Llewellyn, 2000; Dorothy K. Sit, James M. Perel, Joseph C. Helsel, & Katherine L. Wisner, 2008; D. K. Sit, J. M. Perel, J. C. Helsel, & K. L. Wisner, 2008). The conflicting reports may, in part, be due to the complex metabolism route and longitudinal changes in the abundance of these enzyme pathways during gestation and often small sample (patient) sizes within studies. Nevertheless, the consensus within all of these studies highlight the need for careful monitoring of depressive symptoms during the perinatal period.

Furthermore, CYP 2C19 is highly polymorphic and these genetic variabilities have been implicated in the requirement for dose adjustment in use of sertraline and other SSRIs with phenotypes of CYP 2C19 (Bråten et al., 2020; Hicks et al., 2015). Over 30 allelic variants have been identified for CYP 2C19 with the majority of patients being carriers of *CYP 2C19 *1* (extensive metaboliser [EM] trait), **2* (poor metaboliser [PM] trait), *or *17* (ultra-rapid metaboliser [UM] trait) alleles. Further, guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) (https://cpicpgx.org) detail the allele definitions and phenotypic interpretations of CYP 2C19 and their clinical relevance alongside providing

recommendations for genotype-guided dosing of sertraline, namely advocating a dose increase of at least 50 % in PM but no dose adjustment for UM phenotype patients. However, conflicting reports on the impact of specific CYP 2C19 genotypes/phenotypes on sertraline have highlighted the need to investigate the impact of this further on dose adjustments (Bråten et al., 2020).

In the context of post-natal period, SSRIs have been reported to lead to Post Natal Adaptation Syndrome (PNAS). This is, in part, due to their ability to cross the placenta which may result in increased serotonin concentrations in the developing fetus, thus; impacting fetal respiratory, cardiovascular and neurological development (Bérard et al., 2017; Byatt et al., 2013; Zakiyah et al., 2018).

A recent study implemented a pharmacokinetic modelling approach to explore the changes in sertraline concentrations through gestation (George et al., 2020). Whilst they also simulated a decrease in sertraline levels, their study lacked both the use of full body physiological model with a dedicated gestational-age dynamic fetal model and used a limited dataset for validation purposes. Given the limited pharmacokinetic data throughout pregnancy, the predominantly reported decrease in sertraline concentrations, coupled with its complex elimination pathways, we have applied, for the first time, a full body virtual clinical trials pharmacokinetic model to assess the dosing of sertraline throughout gestation to identity necessary dose titrations.

With a focus on the existing guidelines for use of sertraline in CYP 2C19 phenotypes, the primary aim of this study was to: (i) evaluate the influence of gestation on plasma sertraline levels and (ii) provide a clinically relevant dosing titration strategy for CYP 2C19 phenotype status during gestation.

2. METHODS

We utilised the Simcyp Simulator, a physiologically-based pharmacokinetic (PBPK) modelling tool, to conduct virtual clinical trials simulations (Simcyp Ltd, a Certara company, Sheffield, UK, Version 17). Unless otherwise stated, we incorporated mixed genders (50:50) into all simulations. We utilised a four-stage workflow (Figure 1).

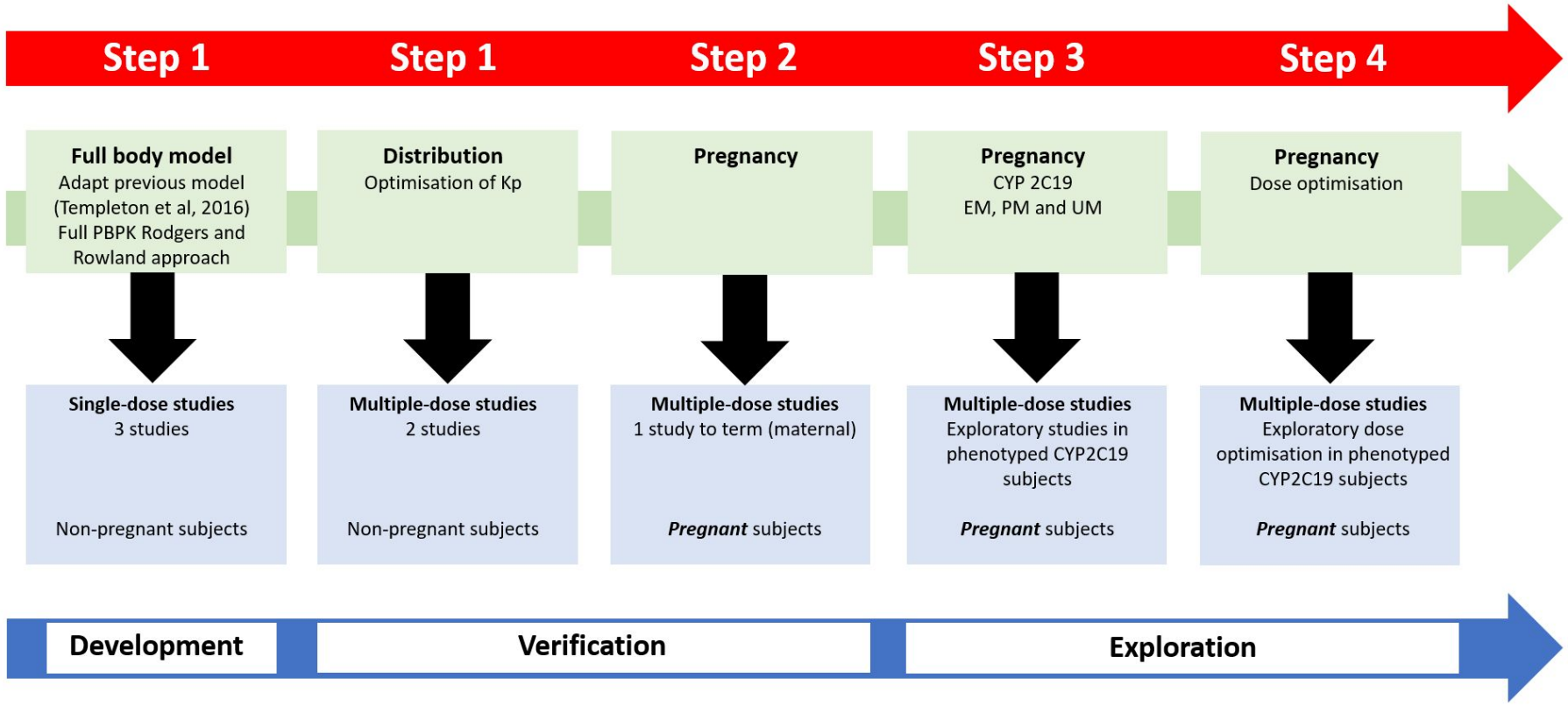


Figure 1. A workflow modelling approach for sertraline

2.1 Step 1: Validation of sertraline

We utilised the Simcyp 'healthy volunteer' (HV) population group for studies with baseline populations consisting of non-pregnant females. For pregnant population groups we used the Simcyp 'pregnancy' population. This population was developed previously by Simcyp researchers and includes gestation dependant changes in physiology, cardiac output, tissue perfusion, blood volume alongside biochemistry modification (e.g. human serum albumin) and enzyme/protein expression (Abduljalil, Furness, Johnson, Rostami-Hodjegan, & Soltani, 2012; De Sousa Mendes et al., 2015; Jogiraju, Avvari, Gollen, & Taft, 2017; Lu et al., 2012). Sertraline is not available within the Simcyp Simulator, however a previous study developed and validated a sertraline compound for use within the Simcyp simulator (Templeton et al., 2016), with modifications made by our group to allow its use during gestation.

In order to apply this previously validated model within the context of our studies, 5 retrospective clinical studies were employed, 4 single dose studies and 1 multiple dose studies: (i) 24 healthy adults (12 male and 12 female) aged between 18-45 years old dosed a single oral dose of 50 mg sertraline (Niyomnaitham, Chatsiricharoenkul, Sathirakul, Pongnarin, & Kongpatanakul, 2009) (ii) 18 healthy subjects administered a single 50 mg oral dose of sertraline (X. Chen, Duan, Dai, & Zhong, 2006); (iii) 5 healthy male volunteers, mean age 26.1 years ± 4.2 years, administered a 50 mg single dose of sertraline (K. M. Kim et al., 2002); (iv) 5 male and 5 female (19-31 years) dosed 100, 200 and 400 mg as a single dose with C_{max} reported (Saletu, Grunberger, & Linzmayer, 1986) and (v) 11 male and 11 female healthy volunteers aged between 18-45 years old administered a 200 mg daily for 30 days, with sampling on day 30 (Ronfeld, Tremaine, & Wilner, 1997); The design of trials within Simcyp were matched to these clinical studies. Simcyp Simulator parameters for sertraline are detailed in the Supplementary Materials (Section 1: Table S1).

2.2 Step 2: Validation of sertraline during pregnancy

In order to apply the developed sertraline model during pregnancy, we conducted further validation using data extracted from a retrospective analysis of therapeutic drug monitoring services in Norway (Westin et al., 2017). This study included 56 pregnant and 52 non-pregnant (female) sertraline plasma concentrations, obtained from 34 women taking an oral dose of 50 mg daily. Importantly, this study reported individualised sample data throughout gestation rather than a central tendency without variance (Dorothy K. Sit et al., 2008), missing patient sample data throughout study or poor sample sizes (M. P. Freeman et al., 2008).

The Simcyp Pregnancy model has been utilised previously to assess changes in plasma concentration in pregnant women (Jogiraju et al., 2017; Ke, Greupink, & Abduljalil, 2018; Olafuyi & Badhan, 2019) and this study represents its application in the context of sertraline for the first time. The Simcyp Pregnancy model changes the physiology of the mother (e.g. tissue volumes) throughout the study period, which allows the model to operate in a dynamic nature, updating the prediction of Vss through the study as a result of updated estimates of the tissue-partition coefficient (Kp), as opposed to using fixed estimates of Kp and Vss.

The Simcyp Pregnancy model does not inherently include longitudinal changes in CYPs 2C19 and 2B6, and these were incorporated based on previous reports of successful implementation within the Simcyp Simulator (Almurjan, Macfarlane, & Badhan; Ke et al., 2018) (Supplementary Materials (Section 2). In order to replicate the study by Westin *et al* (Westin et al., 2017) we utilised a 38-week gestation and 10 x 10 (n=100 subject) study design with sertraline doses of 50 mg daily. Data was collected for every 5th week and presented as the final 24 hours of that period. A similar trial design was implemented for non-pregnant females (baseline).

2.3 Step 3: Impact of CYP 2C19 polymorphism on sertraline plasma concentration during pregnancy

Sertraline plasma concentrations are known to be altered in different CYP 2C19 phenotypes (Hicks et al., 2015). In order to simulate the impact of CYP 2C19 phenotypes in pregnant women, we simulated entirely extensive metaboliser (EM), poor metaboliser (PM) and ultra-rapid metaboliser (UM) populations through revision of the default phenotype distribution to ensure uniform phenotype populations. For each phenotype, CYP 2C19 enzyme abundance was also incorporated and detailed in the Supplementary Materials (Section 2).

Study design implemented a 10x10 trial design with a daily dose of 50 mg once daily throughout gestation and sampling (of plasma concentration) conducted for every 5th week and presented as the final 24 hours of that period. Where appropriate, data was also presented on the final dosing day of the week during trimester 1 (T1: week 10), trimester 2 (T2: week 20) and trimester 3 (T3: week 30).

In the absence of any published data, the default value of 0 pmol/mg was used for CYP 2C19 PM phenotypes within the Simcyp Simulator (Djebli et al., 2015; Gong, Iacono, Iyer, Humphreys, & Zheng, 2018).

2.4 Step 4: Dose adjustment during gestation

To explore approaches to sertraline dose titration during gestation on resultant plasma concentrations, dosing was initiated at 50 mg once daily and increased in weekly increments by 50 mg to a maximum of 300 mg once daily. A proposed therapeutic range was set at 10-75 ng/mL (Bråten et al., 2020). This was based on reports from the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie' (AGNP) suggesting a range of 30-500 nM (Hiemke et al., 2018), equating to a lower limit of approximately 10 ng/mL. The upper limited was defined by Bråten *et al* in relation to the concentration of sertraline occurring

the serotonin transporter (SERT) and being approximately 250 nM (~75 ng/mL) (Bråten et al., 2020; Mauri et al., 2003).

Data was reported for each phenotype studied, namely EM, PM and UM subjects, on the final day of each trimester and presented as the percentage of subjects possessing trough plasma concentrations outside of the therapeutic range (i.e. below 10 ng/mL and above 75 ng/mL).

2.5 Predictive performance

To ensure appropriate predictive performance (Steps 1-2), predictions of pharmacokinetic metrics that were within two-fold (0.5-2.0 fold) of published data was accepted as part of the 'optimal' predictive performance (Edginton, Schmitt, & Willmann, 2006; Ginsberg, Hattis, Russ, & Sonawane, 2004; Parrott et al., 2011). Furthermore, predictions in step 1-2 were also validated using a visual predictive checking (VPC) strategy (U.S. Food and Drug Administration, 2012) when compared to reported data. This approach compared the Simcyp Simulator predicted concentration–time profiles, which consisted of either a mean or median and the 5th and 95th percentiles, against the observed data. A successful validation approach was assumed when Simcyp-predicted results overlapped with the observed data sets (Almurjan et al.; Olafuyi & Badhan, 2019).

2.7 Data and statistical analysis

Retrospective (observed) clinical data was extracted from reported studies using WebPlotDigitizer v.3.10 (http://arohatgi.info/WebPlotDigitizer/). Tabulated (observed) clinical data was utilised as reported in studies, namely mean and standard deviation (Step 1 and 2). Exploratory studies (Step 3 and 4) were reported as median and range, unless otherwise stated. Statistical analysis was conducted using a non-parametric Kruskal-Wallis test with a Dunn's multiple comparison post-hoc test. Significance was confirmed with a $p < 0.05$. All

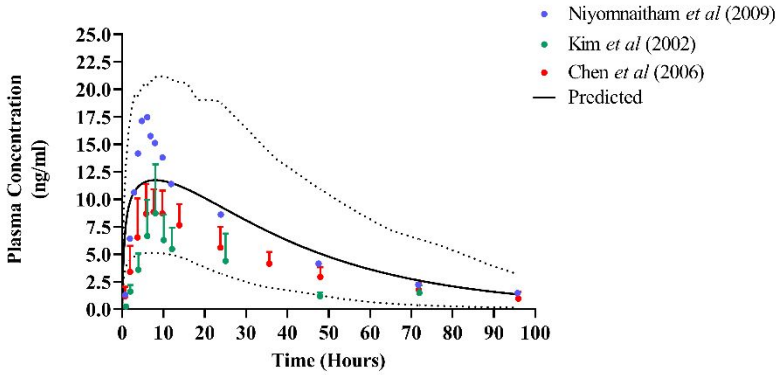
statistical testing was conducted using GraphPad Prism version 8.00 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com).

3. RESULTS

3.1 Step 1: Validation of sertraline

A previously reported sertraline model (Templeton et al., 2016) was adapted, implementing a full-PBPK model in order to appropriately model physiological changes during gestation and their impact upon Vss. The model was validated against 4 single dose studies, 1 multiple dose study and a dose escalation study. The resulting predicted plasma concentration-time profiles successfully predicted single dose (Figure 2A), multiple dose (Figure 2B) and dose escalation studies (Figure 2C). Furthermore, the resultant Simcyp predicted t_{max}, C_{max}, and AUC were within 2-fold of the reported values (Figure 2D) (See supplementary Materials Section 3: Table S1).

(A)



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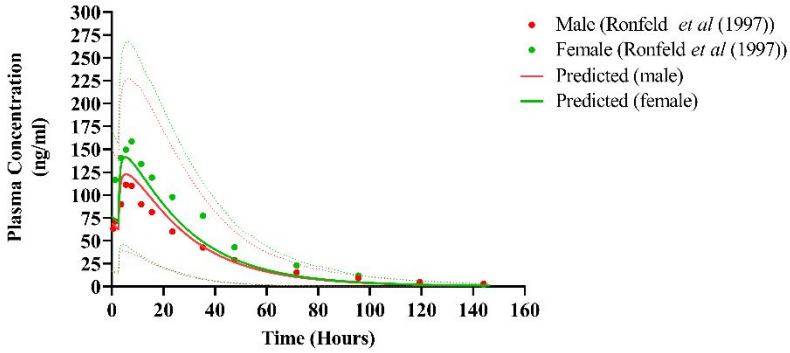
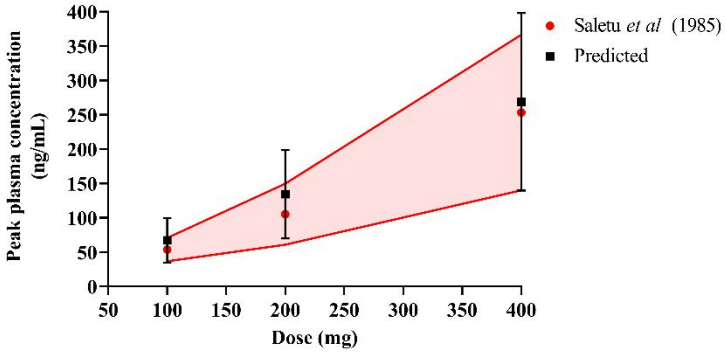
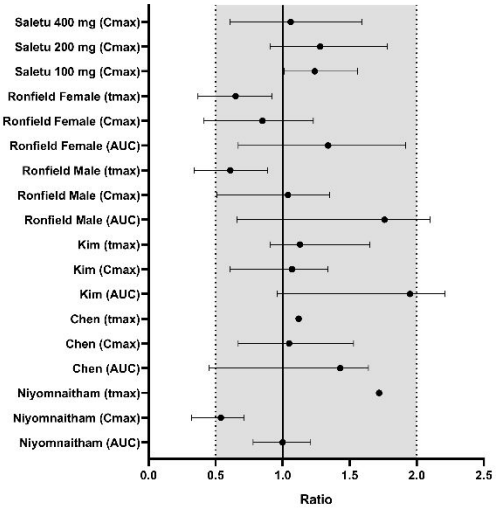


(C)



(D)



233

Figure 2. Simulated sertraline plasma concentrations

(A) Single 50 mg oral doses of sertraline (X. Chen et al., 2006; K. M. Kim et al., 2002; Niyomnaitham et al., 2009); (B) Multiple daily 50 mg oral doses reported on day 30 (Ronfeld et al., 1997) for males (red) and females (green); (C) 100, 200 and 400 mg single doses of sertraline (Saletu et al., 1986); (D) Forest plot showing the predicted mean ± SD over the observed ratio of pharmacokinetic parameters in subjects, with the dotted and shaded area representing the 2-fold range [0.5 to 2] and solid black line the line of unity. For (A) and (B) solid circles represent observed clinical data with error bars indicating standard deviation, solid lines represent predicted mean concentration-time profile and the 5th and 95th percentile range represented by dotted lines. For (C), solid red circles represent observed clinical data with upper and lower red lines indicating standard deviation. Solid black square and error bars indicate mean and standard deviation respectively.

3.2 Step 2: Validation of sertraline during pregnancy

The distribution of simulated sertraline plasma concentrations were similar to the range of observations reported (Westin et al., 2017) during pregnancy (Figure 3). The predicted mean plasma concentration in non-pregnant females (baseline), 16.20 ng/mL ± 10.32 ng/mL, was within 2-fold of that reported, 11.1 ng/mL ± 7.02 ng/mL (Westin et al., 2017). Further when compared to baseline, plasma concentrations decreased for trimester 2 (week 15: 16.13 ng/mL ± 9.71 ng/mL, week 20: 15.01 ng/mL ± 9 ng/mL) and trimester 3 (week 30: 14.41 ng/mL ± 8.59 ng/mL, week 35, 13.68 ng/mL ± 8.13 ng/mL). The decrease from baseline was only statistically significant for week 35 ($p = 0.021$).

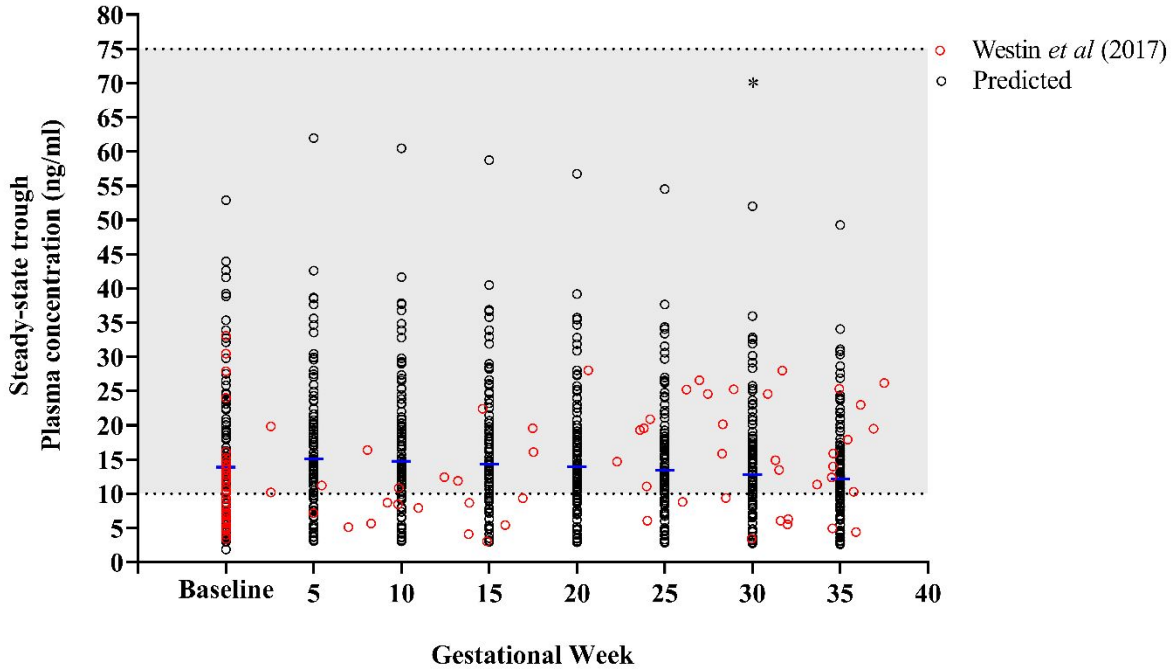


Figure 3. Model predicted and observed plasma concentrations of sertraline throughout pregnancy

Predicted concentrations were obtained from subjects (n=100) administered a 50 mg daily dose and data collected as post-dose (trough concentrations) sampled on the final 24 hours period after dosing and collated every 5-weeks (black open circles). Sertraline concentrations in non-pregnant female are illustrated as 'Baseline'. Red open circles represent pooled (observed) plasma concentrations obtained from a total of 34 subjects. The therapeutic window is represented by the shaded regions between 10 ng/mL to 75 ng/mL. Blue horizontal lines represent mean plasma concentration for the simulated dataset.

3.3 Step 3: Impact of CYP 2C19 polymorphism on sertraline plasma concentrations during pregnancy

CYP 2C19 is highly polymorphic and the primary metabolic pathway for sertraline. Changes in trough concentrations and intrinsic clearance was assessed for baseline and during gestation for CYP 2C19 phenotype subjects, using frequencies reported within Simcyp Simulator (EM: 59 %, PM: 9.2 % and UM: 31.8 %).

The median trough plasma concentration decreased for by 17.2 % (EM, $p < 0.001$), 14.4 % (PM, $p < 0.05$) and 20 % (UM, , $p < 0.001$) by week 30 when compared to baseline (Figure 4) (Supplementary Materials: Section 3 Table S2).

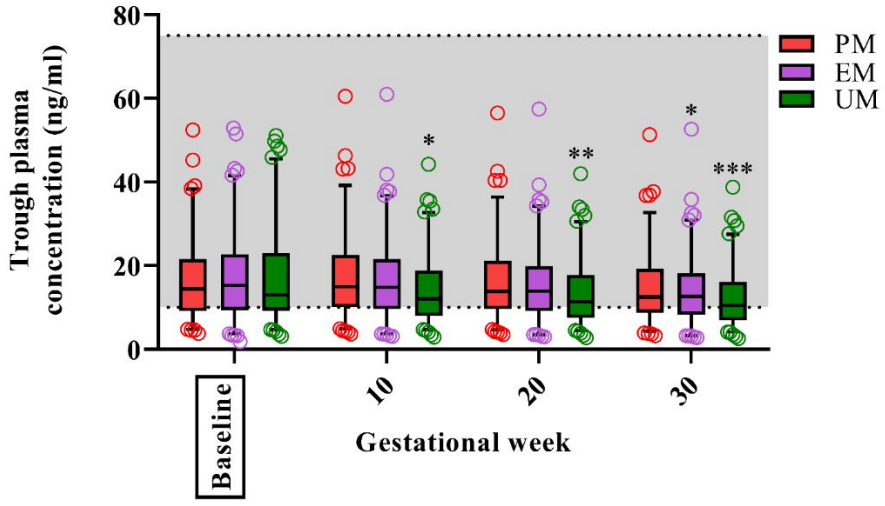


Figure 4. Simulated sertraline trough plasma concentrations for CYP 2C19 polymorphs.

The impact of pregnancy on sertraline trough (C_{min}) plasma concentrations for CYP 2C19 extensive metabolisers (EM) and poor metabolisers (UM) in non-pregnant females (baseline) and throughout pregnancy following a 50 mg once daily dose to 100 subjects per phenotype. Data represent by box and whisker plots with median, 5th and 95th percentiles detailed. *p<0.05, **p<0.01, ***p<0.001.

Despite decreases in trough plasma concentrations throughout gestation, CYP 2C19 intrinsic clearance also decreased. For EMs, a decrease in the median Clint by CYP 2C19 was noticed from the 1st trimester (week 5: 78.4 L/h [17.5-611 L/h]) and continued to decrease in weeks 10 and 15: 68.5 L/h [13.8-533.8 L/h], 63.8 L/h [13.3-513.7 L/h], respectively, when compared to the baseline Clint, 78.4 L/h [17.5-622.1 L/h]. Statistically significant decreases in Clint were apparent from gestational week (GW) 20 onwards when compared to baseline subjects ($p<0.05$) (Figure 5) (Supplementary Materials: Section 4 Table S3).

For UMs, a decrease in the median Clint by CYP 2C19 was also noticed from the 1st trimester (week 5: 97.5 L/h [21.7-721.6 L/h] and continued to decrease in weeks 10 and 15, 90.4 L/h [20.1-671.7 L/h] and 83.3 L/h [18.5-618.7 L/h], respectively, when compared to the baseline Clint, 105.17 L/h [24.5-776.3 L/h]. Statistically significant decrease in Clint was apparent from gestational week (GW) 20 onwards when compared to non-pregnant subjects ($p<0.05$) (Figure 5) (Supplementary Materials: Section 4 Table S3).

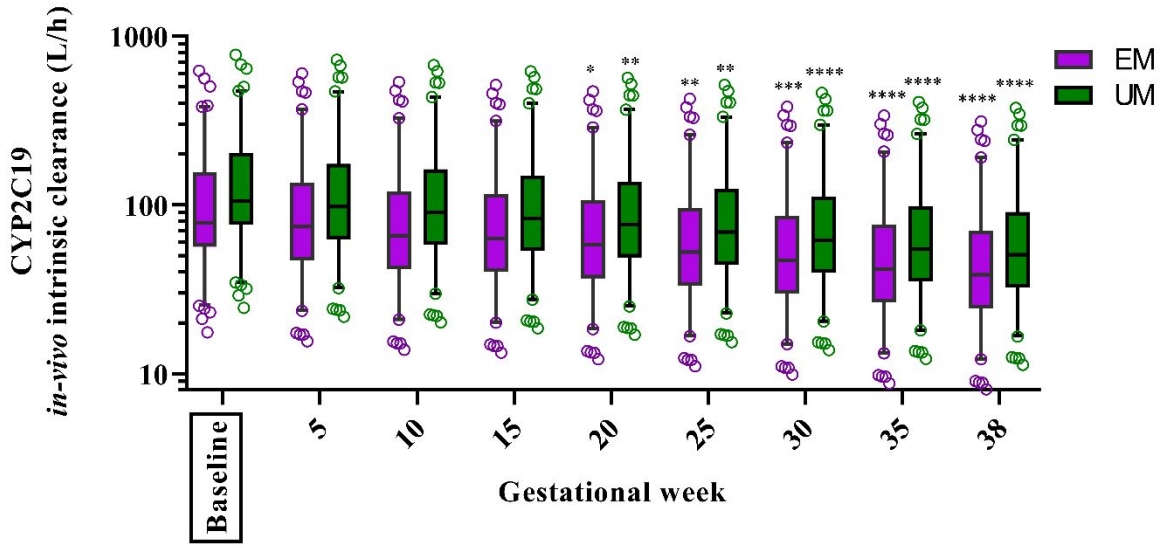


Figure 5. The impact of CYP 2C19 polymorphism on sertraline clearance throughout pregnancy

The impact of CYP 2C19 extensive metaboliser (EM) and ultra-rapid metaboliser (UM) phenotypes on Simcyp predicted sertraline *in-vivo* intrinsic clearance for non-pregnant females (baseline) and during pregnancy, following a 50 mg once daily dose to 100 subjects per phenotype. Data represent by box and whisker plots with median, 5th and 95th percentiles detailed. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

3.4 Step 4: Sertraline dose optimisation

In order to address changes in sertraline concentrations during gestation for CYP 2C19 phenotype subjects, we quantified the percentage of subjects with plasma concentrations outside of the therapeutic range (i.e. below 10 ng/mL and above 75 ng/mL) across a dosing range of 50-300 mg daily.

Regardless of the phenotype, the daily sertraline dose required to maintain trough concentrations within the therapeutic window was above the usual 50 mg/day throughout pregnancy. When attempting to identify an optimal dose, we ensured a balance of a low

percentages of subjects outside of this window, with an optimal dose defined as where no more than 20 % of subjects possessed concentrations outside of the window (Figure 6) (Supplementary Materials: Section 5 Table S4).

For EM and UM, a dose of 100-150 mg daily is suggested to be optimal throughout pregnancy. For PM, a starting dose of 25 mg once daily resulted in a > 60 % of subjects with trough levels below 10 ng/mL across pregnancy (Figure 6). However, a dose of 50 mg once daily resulted in 24 % of subjects possessing trough levels below 10 ng/mL (Figure 6). During trimesters 2 and 3, an increase in dose to 100 mg once daily resulted in less than 10 % of the subjects demonstrating trough levels below 10 ng/mL (Figure 6) (Supplementary Materials: Section 5 Table S4).

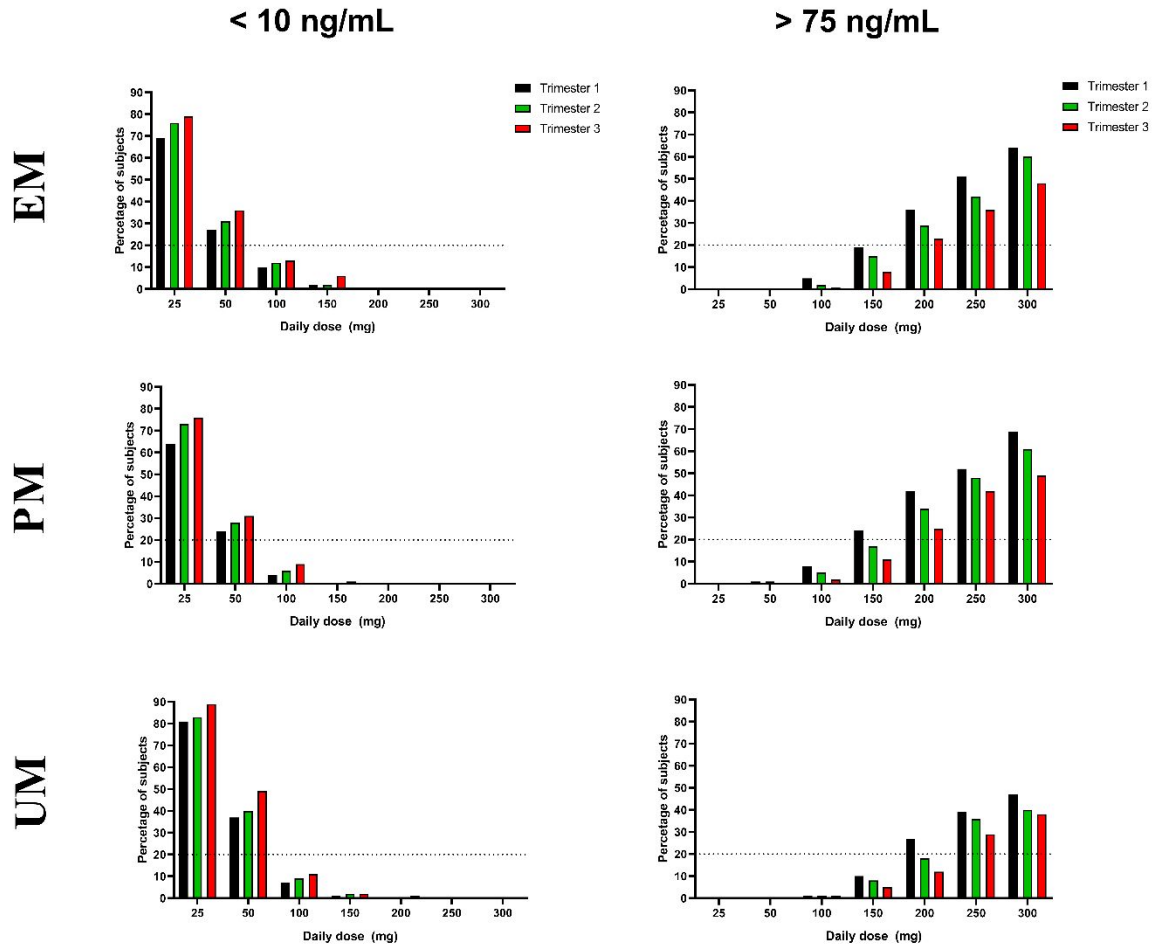


Figure 6. Dose optimisation of sertraline during pregnancy in CYP 2C19 phenotyped subjects

Doses were titrated in increments of 50 mg every 3 days over a range of 50 mg to 300 mg once daily throughout pregnancy. Trough plasma concentrations were reported for the final dosing day of each trimester in specific EM, PM or UM pregnancy population groups. Percentages of subjects with plasma concentration (trough) outside of the therapeutic range (below 10 ng/mL [left panels] and above 75 ng/mL [right panels]) are reported.

4. DISCUSSION

Depression is a leading cause of disability worldwide (World Health Organization, 2008), and is thought to affect more than 20 % of pregnant women (Fisher et al., 2012; Gaynes et al., 2005; Vigod et al., 2016). A key challenge for healthcare professional is the use of pharmacological interventions during pregnancy, which is often informed by balancing the expected benefits for the mother's mental health with the possible risks to the foetus. This decision is further complicated by gestational related alterations in maternal physiology (Isoherranen & Thummel, 2013) which can impact upon the pharmacokinetics of drugs. Often the combined impact of these, in additional to the longitudinal nature of these alterations, make it difficult to extrapolate their impact during clinical practice (Tracy, Venkataramanan, Glover, Caritis, & Units, 2005). To augment the existing empirical approaches to treatment interventions, the application of robust and well validated pharmacokinetic models offers a unique opportunity to apply virtual clinical trials to support medicines optimisation in mental health for special population groups.

Sertraline is metabolised by multiple enzymes, including CYPs 2C19, 2B6, 2C9, 3A4 and 2D6. Confounding the use of sertraline in pregnancy, is the gestational alterations in maternal CYP 2C19 activity, which has been determined to decrease by 62 % and 68 % during trimester 2 and 3 respectively (McGready, Stepniewska, Edstein, et al., 2003; McGready, Stepniewska, Seaton, et al., 2003; Ward et al., 1991). Despite this decrease, several confounding studies have noticed either an apparent decrease (M. P. Freeman et al., 2008; Hostetter et al., 2000; D. K. Sit et al., 2008) or increase (Westin et al., 2017) in sertraline plasma concentrations during gestation.

In this study, we have applied virtual clinical trials dosing of sertraline throughout pregnancy, to identity suitable dose titration necessary to support therapeutically maintained sertraline plasma concentrations in the mother throughout pregnancy.

We adapted a previously published sertraline model (Templeton et al., 2016) to allow its use within the context of gestation, and this was fully validated with both single and multiple dose studies in both pregnant and non-pregnant subjects, with predictions to 2-fold of those reported (Figure 2) (Supplementary Materials: Section 3 Table S1) and spanning a similar range within the population studies (Figure 2). However, a wider AUC range in the predicted-observed ratios (Figure 2D), although still within 2-fold, are thought to be a reflection of the complexity associated with the metabolism of sertraline, namely CYPs 2C9, 2C129, 2B6, 2D6 and 3A4 and hence the associated contribution towards inter-individual variability. The variance in AUC from clinical studies (measured as mainly the standard deviation) was broadly similar to those simulated within our studies (See Supplementary Materials Section 3).

A recent report by Westin *et al* (Westin et al., 2017) highlighted sertraline plasma concentration throughout gestation in 34 subjects. This was used as the basis for validation of the pregnancy PBPK model. The resulting mean plasma concentrations in non-pregnant subjects (16.20 ng/mL ± 10.32 ng/mL) were within 2-fold of those reported (Westin et al., 2018) and also demonstrated a similar predicted range to that reported (Figure 3). Furthermore, we demonstrated a decrease in mean plasma concentration throughout pregnancy with a significant decrease in GW35 ($p<0.05$) compared to baseline (Figure 3). On the contrary, a 10 %, 36 % and 68 % increase in plasma concentration were reported by Westin *et al* (Westin et al., 2017) during trimesters 1-3 respectively. Other studies have identified a similar decrease to that reported here (M. P. Freeman et al., 2008) (Dorothy K. Sit et al., 2008), however Westin

et al (Westin et al., 2017) included individualised sample data throughout gestation rather than a central tendency without variance (Dorothy K. Sit et al., 2008), missing patient sample data throughout the study or utilising poor sample sizes (M. P. Freeman et al., 2008). Nonetheless, to further examine the reported disparity in clinical observations, we assessed changes in trough plasma concentrations and intrinsic clearance as a result of population variability in the phenotypes of one of the primary CYP isozyme responsible for sertraline metabolism, namely CYP 2C19. In all tested phenotypes, the intrinsic clearance decreased throughout pregnancy, mirroring decreases in CYP 2C19 activity, the largest significant difference in clearance being noticed in trimester 3 (Supplementary Materials: Section 4 Table S3).

This decrease in clearance was expected to increase sertraline trough plasma concentrations as observed by Westin *et al* (Westin et al., 2017). On the contrary, trough plasma concentrations for EMs and UMs decreased during gestation with the greatest significant decrease occurring in trimester 3 (Figure 6), which concurred with a range of other reports (M. P. Freeman et al., 2008; Schoretsanitis et al., 2020; D. K. Sit et al., 2008; Tracy et al., 2005; Ververs et al., 2009). This decrease has been associated with an increase in the key female hormones estradiol and progesterone throughout pregnancy, with concentrations reaching up to 100 nM and 1 μM for estradiol and progesterone, respectively, at term. These levels are significantly greater than those during menstruation (< 50 nM) (Cunningham, Leveno, Bloom, Spong, & Dashe, 2014; Holinka, Diczfalusy, Bennink, & biology, 2008). Such female hormones are known to be activators for basic helix-loop-helix transcription factors (e.g. aryl hydrocarbon receptor; AhR) or nuclear hormone transcriptional regulators (constitutive androstane receptor, CAR; pregnane X receptor, PXR; estrogen receptor, ER), which contribute to the induction of a variety of CYP isoforms and enhanced drug clearances (H. Chen, Yang, Choi, Fischer, & Jeong, 2009; Jeong, Choi, Song, Chen, & Fischer, 2008). However, the metabolic breakdown of sertraline is complicated, and includes CYPs 2B6, 2C9, 2C19, 2D6, and 3A4. The

contribution of each isozyme has proven difficult to determine *in-vivo*, however the variable up- or down-regulation of CYP isozyme expression during gestation (Abduljalil & Badhan, 2020) may contribute to the disparity observed in some studies (Westin et al., 2017). For example, the approximate 2-fold decrease in 2C19 activity coupled with approximately 2-fold increase in 2B6 activity by trimester 3 may negate the overall impact of each pathway, in preference to changes in other physiological factors such as increases in total body water. Furthermore, the concomitant decrease in albumin is likely to cause the observed increase in sertraline plasma unbound fraction and hence increase the volume of distribution, extending the half-life and reducing sertraline plasma levels. To confirm this, a global sensitivity analysis (GSA) was implemented to examine the combined influence of albumin levels, CYPs 2C19 and 2B6 abundance on Cmax, AUC, Cl and Vss (Supplementary Materials: Section 6) within the model. The resulting model sensitivity rankings (Supplementary Materials: Section 6 Table S5), confirmed the sensitivity of the model to changes in human serum albumin levels throughout gestation and primarily in trimester 3 (Supplementary Materials: Section 6 Table S6). Given that sertraline is highly protein bound, the decrease in albumin during pregnancy would be significant driver for reduced plasma levels and an extension of the half-life (Little & Gynecology, 1999), potentially more so that the impact of CYP isozyme gestational changes.

At present, there is a paucity of studies exploring the impact of CYP 2C19 phenotypes on sertraline levels during pregnancy. A recent dosing guideline for sertraline which considered CYP 2C19 phenotypes has been published (Hicks et al., 2015). However, it is not clear whether the proposed guidelines are relevant to pregnant women. Given the importance of the phenotype of the subject on gestational sertraline levels, we next examined the changes in the trough levels in relation to the therapeutic range of sertraline under a standard 50 mg daily dosage of sertraline (Bråten et al., 2020). As expected, the UM phenotypes demonstrated the

largest number of subjects below 10 ng/mL (Supplementary Materials: Section 5 Table S4), whereas for the PM group, this was predicted to be in the range of 24-31 %.

Finally, for all phenotypes (EM, PM and UM), dose titrations were required to daily doses that were typically in excess of the 50 mg dose throughout pregnancy. For EM and UM, a dose escalation to 100-150 mg daily is suggested to be optimal through pregnancy. For PM, a dose of 50 mg during the first trimester followed by a dose increase in trimesters 2 and 3 to 100 mg is suggested to be optimal. Furthermore, the doses suggested within this study are within the range clinical utilised and significantly below the know toxicity range in adults (> 4000 mg/daily) (Lau & Horowitz, 1996). The return of maternal sertraline plasma levels would be needed post-natally and although this is not possible to simulate within Simcyp, tapering the dose of sertraline by 50 mg per 5-7 days is recommended to avoid withdrawal syndrome (Shelton & Richard, 2001). Furthermore, although there is very little published studies reporting pharmacodynamic changes during pregnancy for sertraline, the current approaches for the studies during pregnancy focus primarily on the clinicians role in the dose titration based on empirical changes in the psychiatric state of the patient (Ornoy & Koren, 2019). In addition, although clinicians routinely monitor drug pharmacodynamics by directly measuring physiological indices of therapeutic responses, the link between (unbound) plasma levels and clinical response is not well established for sertraline (Bergink et al., 2011; Cox, Holden, & Sagovsky, 1987; Sachs, Guille, & McMurrich, 2002). Further, any attempt to relate unbound levels to a pharmacodynamic effect would need to further consider that the resultant central effects would be governed by the blood-brain barrier, which acts as a permeability barrier to any resultant central effects on reuptake of monoamines into the presynaptic neurones. Further work is needed to address the reductions in sertraline plasma concentration through gestation on the resultant maternal pharmacodynamic effects on mood stability, in order to fully translate the results presented within this manuscript to clinical practice.

A key benefit of the pregnancy PBPK approach highlighted within our study, is the ability to incorporate key gestational changes in the physiology of the mother, for example the highlight reduction in plasma albumin and increase in maternal volume, which can be coupled with a mechanistic description of the activities of metabolising enzyme to enable disentangling what would otherwise be clinically complicated relationships.

5. CONCLUSION

Any decision to withdraw or continue with antidepressant therapy perinatally is challenging for both maternal and fetal health. A key paradigm is the balance between the benefit of continuing treatment and the risk drug-related toxicity to the developing embryo/foetus.

Confounding treatment during gestation, are longitudinal maternal physiological alternations which alter the requirements for dosing. Furthermore, the susceptibility of CYP 2C19 to polymorphisms only increases the complexity in prescribing decisions.

Our results demonstrated that dose titrations are required throughout pregnancy, with UM subjects being of concern and requiring at least double the standard dose by trimester 3, to support on-going maintenance of plasma sertraline concentrations to within the therapeutic range.

This study has highlighted a key role for the use of pharmacokinetics to allow pragmatic exploration of dosing regimens within a perinatal setting, to support the reduction in risk of treatment relapse due to inappropriate dosing.

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Declaration of conflicting inflects

The Author(s) declare(s) that there is no conflict of interest.

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