Received: 22 January 2024 | Revised: 17 May 2024 | Accepted: 17 June 2024

DOI: 10.1111/bcp.16177

ORIGINAL ARTICLE

A population pharmacokinetic model for sertraline in women during the perinatal period—A contribution from the ConcePTION project

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Funding information
Innovative Medicines Initiative 2 Joint Undertaking, Grant/Award Number: 821520; European Union's Horizon 2020; EFPIA; Swiss National Science Foundation, Grant/Award Number: 320030_135650

Abstract

Aims: Sertraline is frequently prescribed for mental health conditions in both pregnant and breastfeeding women. According to the limited available data, only small amounts of sertraline are transferred into human milk, yet with a large amount of unexplained interindividual variability. This study aimed to develop a population pharmacokinetic (popPK) model to describe the pharmacokinetics of sertraline during the perinatal period and explain interindividual variability.

Methods: Pregnant women treated with sertraline were enrolled in the multicenter prospective cohort SSRI-Breast Milk study. A popPK model for sertraline maternal plasma and breast milk concentrations was developed and allowed estimating the milk-to-plasma ratio (MPR). An additional fetal compartment allowed cord blood concentrations to be described. Several covariates were tested for significance. Ultimately, model-based simulations allowed infant drug exposure through placenta and breast milk under various conditions to be predicted.

Results: Thirty-eight women treated with sertraline were included in the study and provided 89 maternal plasma, 29 cord blood and 107 breast milk samples. Sertraline clearance was reduced by 42% in CYP2C19 poor metabolizers compared to other phenotypes. Doubling milk fat content increased the MPR by 95%. Simulations suggested a median daily infant dosage of 6.9 μg kg^{-1} after a 50 mg maternal daily dose,

Alice Panchaud and Monia Guidi contributed equally to this work.

The authors confirm that the Principal Investigator for this paper is Alice Panchaud and that she had direct clinical responsibility for patients.

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representing 0.95% of the weight-adjusted maternal dose. Median cord blood concentrations could range from 3.29 to 33.23 ng mL^{-1} after maternal daily doses between 25 and 150 mg.

Conclusions: Infant exposure to sertraline, influenced by CYP2C19 phenotype and breast milk fat content, remains low, providing reassurance regarding the use of sertraline during pregnancy and breastfeeding.

KEYWORDS
breastfeeding, infant exposure, population pharmacokinetic modelling, pregnancy, sertraline

1 | INTRODUCTION

Mental health conditions affect 10% of pregnant women and 13% of breastfeeding women according to the World Health Organization (WHO).[1] To ensure optimal management of these disorders in the perinatal period, pharmacological treatments are often required.[2,3] Selecting the appropriate medication in this population is challenging, as it must be safe for the child and effective for the mother. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant drugs for pregnant and breastfeeding women.[4,5] Among the available SSRIs, escitalopram and sertraline have been preferred due to their favourable safety profiles. Notably, sertraline has gained particular attention, especially during the third trimester of pregnancy, due to its relatively lower risk of perinatal complications in the newborn, such as preterm birth, low birth weight and admissions to the neonatal intensive care unit, compared to other antidepressants.[4,6]

Understanding the pharmacokinetic (PK) properties of sertraline can aid in understanding its safety profile. Sertraline is given in a dose range of 50–200 mg day^{-1}, in which it has linear PK properties.[7] The drug is characterized by slow absorption, an extensive volume of distribution exceeding 20 L kg^{-1}, a clearance typically ranging between 1.09 and 1.41 L h^{-1} kg^{-1}, and a half-life ranging between 22 and 32 h.[8–10] Moreover, sertraline also exhibits a high degree of protein binding, approaching 98%. The metabolism of sertraline occurs primarily in the liver, where it undergoes biotransformation into its active metabolite, desmethylsertraline, which possesses approximately 10% of its parent drug's biological activity.[8,11] This metabolic process involves multiple cytochrome P450 (CYP450) enzymes, with CYP2C19 and CYP2B6 playing particularly significant roles in sertraline biotransformation and elimination.[8,12–14] Individuals classified as CYP2C19 poor metabolizers exhibit a significantly slower rate of metabolite formation compared to those with other CYP2C19 phenotypes. Consequently, this slower metabolism leads to an increased exposure to sertraline and contributes to the large interindividual variability observed within the general population.[8] CYP2B6 genetic variation has also recently been associated with sertraline exposure.[15]

According to existing literature, sertraline has been observed to transfer both through the placenta and into breast milk.[11,16–27] However, the concentrations measured in cord blood and breast milk were relatively low. In summary, following doses ranging from 25 to 200 mg of sertraline, the milk-to-maternal plasma concentration (M/P) ratio has been found to vary between 0 and 5.2 with values often exceeding 1, the latter suggesting higher concentrations of sertraline in breast milk than in maternal plasma. For an exclusively breastfed infant consuming 150 mL kg^{-1} of milk daily, the daily intakes of sertraline dose were ranging between 0.5 and 44 μg kg^{-1}, representing 0.07% to 3.2% of the maternal weight-adjusted dose.[28] Although the percentage of maternal weight-adjusted dose, that is, the relative infant dose (RID), remains below 5% in all cases, a large interindividual variability has been observed in the transfer of sertraline into breast milk, potentially influenced by various factors including milk composition or sampling procedures.[11,16–22] In breastfed infants, sertraline concentrations were mostly below 2 μg L^{-1}. The highest concentration detected in a breastfed infant was 13 μg L^{-1} after a maternal dose of 150 mg per day.[11,16–19,29–32] Regarding the transfer of sertraline to the fetus, a mean (range) cord blood-to-maternal plasma concentration ratio (C/P

What is already known about this subject

- According to the available data, only small amounts of sertraline are transferred into breast milk and cord blood.
- However, these data show significant unexplained interindividual variability.

What this study adds

- This novel popPK model complements existing successful models for drug transfer into breast milk. It highlights the effectiveness of this approach in characterizing the drug pharmacokinetics in cord blood and breast milk, assessing interindividual variability and identifying covariates responsible for such variability.
- This model allows the identification of two covariates, namely, CYP2C19 phenotype and fat content in breast milk, influencing infant exposure to sertraline.
- However, infant exposure is low and reassuring regarding the use of sertraline during pregnancy and breastfeeding.

ratio) of approximately 0.41 (0.14–1.2) has been reported, indicating low yet very variable transfer to the fetus.[23–27] Currently, the underlying reasons for these interindividual variabilities in both pregnant and breastfeeding women remain to be fully elucidated.

A population pharmacokinetic (popPK) approach, requiring a limited number of per-patient samples from a large patient population, represents an appealing method to assess the interindividual variability of sertraline transfer into the fetus and in breast milk.[33] This approach is particularly valuable since collecting multiple cord blood samples over time and obtaining multiple milk samples from breastfeeding mothers is challenging.

The objective of this study was to describe the PK of sertraline in women with a mental health condition during the perinatal period using a popPK modelling approach. It aimed to evaluate multiple genetic, environmental and demographic factors to explain interindividual variability in sertraline plasma, umbilical cord and milk concentrations. Finally, model-based simulations were used to determine potential infant exposure to sertraline through the placenta and breast milk under various conditions.

2 | METHODS

2.1 | Study population

The SSRI-Breast Milk study (clinical trials identification number: NCT01796132) aimed to assess the clinical and PK implications of antidepressants during pregnancy and breastfeeding. Pregnant women treated with sertraline or any other SSRI who intended to breastfeed their infant and planned to deliver at the maternity unit of the Hospitals of Lausanne, Geneva, Morges, Lyon or Nancy were included in the study. The study received approval from local ethics committees and local health authorities in both Switzerland and France in 2012 and 2013. Prior to participating in any phase of the study, written informed consent was obtained from all enrolled women.

Participants to the SSRI-Breast Milk study were asked to provide a blood sample paired with a cord blood sample on the day of delivery. Additionally, one maternal blood sample was collected and paired with a foremilk and a hindmilk sample at 1 and 4 to 6 weeks postpartum taken at the convenience of the woman after the sertraline dose. The time after doses and steady-state conditions were self-reported by each woman during interviews conducted by midwives.

2.2 | Sample collection and analytical methods

Maternal and umbilical cord blood samples (5 mL each) were collected by venepuncture using ethylenediaminetetraacetic acid (EDTA)-K tubes. Plasma samples were extracted through centrifugation and subsequently stored at −20°C. Breast milk samples (5–10 mL) were obtained in falcon tubes, employing either manual expression or an electrical pump, and were also stored at −20°C. Prior to a feeding, a 5 mL sample was collected by the woman representing a foremilk sample, and another 5 mL sample was collected after the same feeding. Sertraline concentrations in maternal plasma, cord blood and breast milk samples were measured using validated high performance liquid chromatography coupled to electrospray mass spectrometry methods, as previously described.[34,35] The lower limit of quantification for sertraline was established at 1 ng mL^{-1} in plasma and 5 ng mL^{-1} in breast milk. Additionally, breast milk samples were analysed for their fat, protein, carbohydrate and calorie content using a Human Milk Analyzer (Miris, Uppsala, Sweden).

2.3 | Genotyping

Genomic DNA was extracted from EDTA-K blood samples collected either at delivery or at Week 1 post-partum. A TaqMan-Assay-based real-time polymerase chain reaction, previously described, was employed to analyse several single nucleotide polymorphisms (SNPs) including *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17*, *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*6*, *CYP3A4*22*, *CYP3A5*3* and *POR*28*.[36,37] Additionally, a TaqMan copy number assay was used to detect duplication/multiplication of the *CYP2D6*×N* and *CYP2D6*5* gene deletion. Based on their CYP2C19 genotype, patients were classified into four predicted phenotypes: poor metabolizer (PM) if they carried two no function alleles (**2/*2*, **3/*3*, **2/*3*), intermediate metabolizer (IM) if they carried one no function allele (**1/*2*, **1/*3*, **2/*17*, **3/*17*), normal metabolizer (NM) if they carried two normal function alleles (**1/*1*) and ultrarapid metabolizer (UM) if they carried one or two increased function alleles (**1/*17*, **17/*17*). Similarly, four different predicted phenotype groups were made for the CYP2D6 genotype: PM if they carried two no function alleles *CYP2D6*3*, **4*, **5* and **6* (e.g., **4/*4*, **4/*5* or **4/*6*), IM if they carried one normal function and one no function allele (e.g., **1/*3*, **1/*4*, **1/*5*), NM if they carried two normal function alleles (**1/*1*) and UM if they carried one normal function allele and an increased number of gene copies (**1/*×N*). Actual genotypes were used for CYP3A4 (**1/*1*, **1/*22*, **22/*22*), CYP3A5 (**1/*1*, **1/*3*, **3/*3*) and POR (**1/*1*, **1/*28*, **28/*28*).

2.4 | Population pharmacokinetic analysis

Nonlinear mixed-effects modelling implemented with NONMEM (version 7.4, ICON Development Solutions, Ellicott City, MD, USA) and supplemented with the Perl-speaks-NONMEM toolkit (PsN, version 5.3.0) and Pirana interface (version 2.9.3) was used to describe sertraline concentrations in maternal, cord blood and breast milk. Specifically, the FOCE-I algorithm with the subroutine ADVAN6 was selected for this analysis. Graphical and statistical explorations, along with virtual population generation were performed using R (version 4.2.2).

2.4.1 | Structural and statistical model development

A stepwise procedure was used to find the popPK model that best fits the sertraline data. First, one- and two-compartment models with

various absorption processes were compared. Then, the transfer of sertraline to breast milk was characterized either by adding a milk compartment directly exchanging the drug with the plasma compartment with a milk volume of 0.125 L to prevent identifiability issues[38–40] or by using a scaling factor between plasma and milk concentration profiles assuming to reflect the MPR.[41,42] Finally, a fetal compartment of negligible volume was scaled to the central compartment and linked to it via a first-order process to describe cord blood concentrations.[39] Interindividual variability (IIV) in the PK parameters was estimated using an exponential error model. Additive, proportional and mixed models were explored to capture the residual unexplained variability (RUV).

2.4.2 | Covariate models

The influence of genetic, demographic and environmental covariates on the final base model parameters was investigated using a forward insertion/backward deletion approach. The following covariates were considered for apparent sertraline clearance (CL_{SERT}/F): maternal age, body weight, moment of blood sampling (categorized as during labour, after delivery, first week postpartum or 1 month after delivery) and CYP2C19, CYP2D6, CYP3A4, CYP3A5 and POR polymorphisms.

Regarding drug transfer into breast milk, factors including feeding occasion (foremilk or hindmilk) (FEED), the time postpartum (first week postpartum or fourth week postpartum) (MOM), and the composition of breast milk in terms of fat (FAT), protein (PROT), carbohydrate (CARBO) and calorie content (ENERGY) were considered as potential influencing covariates. In the absence of an IIV on the PK parameters, covariates with a known a priori relationship to a PK parameter were tested. A linear function was applied to continuous covariates, involving normalization and centring on their median population values. Dichotomous covariates were represented as 0 or 1. For discrete variables with more than two categories, either a fixed effect was assigned to each group (rich model), or to regrouped categories (reduced model).

The most common predicted phenotype or genotype as appropriate was assigned to the single patient with missing genetic information. To manage missing values for FAT, a multiple imputation method was employed,[43] generating 20 datasets and incorporating the feeding occasion and the time postpartum as covariates for plausible numbers generation. The median value from these 20 datasets was used to replace the FAT missing values in our dataset. Missing data for other continuous covariates were replaced by the median value.

2.4.3 | Parameter estimation and model selection

Differences in the NONMEM objective function (OFV) were used to discriminate two nested models. Unless specified otherwise, a difference in OFV [$\Delta OFV = OFV_{test\ model} - OFV_{initial\ model}$] of at least -3.84 (χ^2 distribution with 1 degree of freedom, $P < .05$) was considered statistically significant for the addition of one extra parameter during model building and forward covariate insertion and 6.63 (χ^2 distribution with 1 degree of freedom, $P < .01$) for backward deletion steps. For non-hierarchical models, the Bayesian Information Criterion (BIC) was employed to compensate for improved fit due to increased model complexity, considering a drop of at least 2 relevant for the selection of the most complex model.[44]

Additionally, goodness-of-fit plots, the precision of parameter estimates and reductions in IIV were considered for model quality assessment.

2.4.4 | Model evaluation

The final popPK model was evaluated using a non-parametric bootstrap procedure with replacement to generate 2000 new datasets. The resulting PK parameters were summarized as median along with 2.5th and 97.5th percentiles (95% confidence interval [95% CI]) and compared to the estimations obtained from the original model. In addition, prediction-corrected visual predictive checks (pc-VPC) were conducted for breast milk, plasma and cord blood concentrations by running 1000 simulations based on the final model using the PsN toolkit. The observed 5th, 50th and 95th percentiles were plotted alongside their respective simulated 95% CI values to assess model's predictive performance.

2.4.5 | Simulation of drug concentrations and prediction of infant exposure

Maternal plasma, breast milk and cord blood concentrations of sertraline at steady state were simulated for various dosage regimens (25, 50, 75, 100, 125 and 150 mg day^{-1}) in 10 000 mothers based on the final popPK model with IIV as a function of the retained influential factors. Half of the women were categorized into CYP2C19 PM, while the other half as CYP2C19 non-PM. A single value of FAT was randomly assigned to each woman following a uniform distribution with a minimum value of 0.5 g 100 mL^{-1} and a maximum value of 7.4 g 100 mL^{-1}, to mimic the FAT distribution in our population. Each woman was assigned a random breastfeeding frequency and interval following the last dose intake to generate breastfeeding time during the day. The mean frequency was set at 11 feedings per day, ranging between 6 and 18 times a day.[45] Sertraline concentration in milk was then predicted at each breastfeeding time according to mothers' characteristics. Subsequently, the infant's daily dose was calculated using the following equation:

$$\text{Infant daily dose} = \sum_{i=1}^{n} C_{milk}i * V_{milk} \quad (1)$$

where $C_{milk}\ i$ (ng mL^{-1}) represents the simulated sertraline concentration at the ith feeding time after administration of sertraline to the mother, n is the daily feeding frequency and V_{milk} is the volume of milk ingested by a breastfed infant during a feeding occasion. A weight-

adjusted daily milk intake of 150 mL kg^{-1} day^{-1} divided by the feeding frequency was used as a typical V_{milk} for simplicity purposes.[28]

The RID was calculated as a percentage for clinical relevance for all dosage regimens.[28] Another valuable parameter for evaluating infant exposure is the adult dose equivalent (ADEQ), a less commonly known metric. The ADEQ quantifies the virtual number of standard tablets that an infant would ingest over 6 months of exclusive breastfeeding. The ADEQ is estimated by dividing the cumulative infant daily dose over 6 months by a standard adult daily dose (50 mg for sertraline) assuming an average child weight of 6 kg.

Lastly, the C/P ratio was computed for each simulated woman across the dosage range of 25–150 mg day^{-1}.

3 | RESULTS

3.1 | Study population and data

A total of 89 maternal blood samples (i.e., 34 at delivery, 35 at Week 1 postpartum, and 20 at Weeks 4–6 postpartum) were collected from 38 mothers taking sertraline included in the SSRI-Breast Milk study. These women provided 107 breast milk samples, 67 of which were collected at Week 1 and 40 at Week 4. Additionally, 29 cord blood samples were collected at delivery. Sertraline concentrations *vs.* time after dose are presented in Figure S1. Notably, two participants were excluded from the popPK analysis due to undetectable sertraline concentrations, likely attributable to non-adherence to the treatment regimen. The median daily dose of sertraline was 50 mg, with doses of 25 mg ($n = 10$), 50 mg ($n = 23$), 75 mg ($n = 1$), 100 mg ($n = 3$), 125 mg ($n = 1$) and 150 mg ($n = 2$). Table 1 describes the demographic and baseline characteristics of the women included in the study.

3.2 | Structural models

Sertraline plasma concentrations were best described by a one-compartment model with first-order absorption and elimination ($\Delta OFV = -1.72$, $P > .05$ compared to a two-compartment model). Assignment of IIV on CL_{SERT}/F ($\Delta OFV = -43.06$, $P < .05$), but neither on apparent volume of distribution (V_{SERT}/F) nor on absorption rate (ka_{SERT}) ($\Delta OFV \geq -2.55$, $P > .05$), improved model fit. The alternative models used to describe simultaneously plasma and milk concentrations yielded similar parameter estimations. Since none of the models was statistically superior to the other ($\Delta BIC = 0.331$), the simpler parametrization with the MPR scaling factor was retained for further analysis. The addition of an IIV on MPR did not significantly improve the fit ($\Delta OFV = -2.97$, $P > .05$). Finally, a third compartment of negligible volume adequately fit the cord blood data, without altering the maternal plasma compartment. Data did not support the inclusion of an IIV on the transfer rates between maternal plasma and cord blood (k_{MC} and k_{CM}). Proportional error models were retained to describe maternal plasma, breast milk and cord blood RUV. Figure 1 represents the final structural model. A template of the code is available in Supporting information S2.

3.3 | Covariate models

Univariate analyses for the model that included plasma and milk concentrations revealed a significant association between CYP2C19

TABLE 1 Demographic and baseline characteristics of the study population.

Parameter	Value
Treatment indication[a], *n* (%) (*n* = 29)	
Depressive disorders	19 (47.5%)
Anxiety disorders	12 (30.0%)
Obsessive-compulsive disorders	1 (2.5%)
Other disorders	8 (20.0%)
Age (years), median (range) (*n* = 38)	34 (22–39)
Bodyweight (kg), median (range)	
Term pregnancy ($n = 23$)	73.0 (51.9–103.0)
First week post-partum ($n = 27$)	71.4 (50.0–107.0)
First month post-partum ($n = 15$)	64.0 (49.0–93.0)
CYP2C19 predicted phenotype, *n* (%) (*n* = 35)	
Poor metabolizer (PM)	2 (6%)
Intermediate metabolizer (IM)	5 (14%)
Normal metabolizer (NM)	15 (43%)
Ultrarapid metabolizer (UM)	13 (37%)
CYP2D6 predicted phenotype, *n* (%) (*n* = 35)	
Poor metabolizer (PM)	5 (14%)
Intermediate metabolizer (IM)	9 (26%)
Normal metabolizer (NM)	18 (51%)
Ultrarapid metabolizer (UM)	3 (9%)
CYP3A4 genotype, *n* (%) (*n* = 35)	
**1/*1*	32 (91%)
**1/*22*	3 (9%)
CYP3A5 genotype, *n* (%) (*n* = 35)	
**1/*1*	0 (0%)
**1/*3*	3 (9%)
**3/*3*	32 (91%)
POR genotype, *n* (%) (*n* = 35)	
**1/*1*	18 (51%)
**1/*28*	14 (40%)
**28/*28*	3 (9%)
Breast milk (foremilk) (*n* = 26)	
Fat content (FAT) (g 100 mL^{-1})	1.9 (1.1–4.8)
Protein content (PROT) (g 100 mL^{-1})	1.6 (0.0–4.3)
Carbohydrate content (CARBO) (g 100 mL^{-1})	6.1 (1.2–7.9)
Calorie content (ENERGY) (g 100 mL^{-1})	49.0 (1.0–75.0)
Breast milk (hindmilk) (*n* = 24)	
Fat content (FAT) (g 100 mL^{-1})	2.7 (0.5–7.2)
Protein content (PROT) (g 100 mL^{-1})	1.5 (0–2.6)
Carbohydrate content (CARBO) (g 100 mL^{-1})	5.9 (0.9–7.8)
Calorie content (ENERGY) (g 100 mL^{-1})	50.0 (17.0–93.0)

[a]Women could have multiple treatment indications.

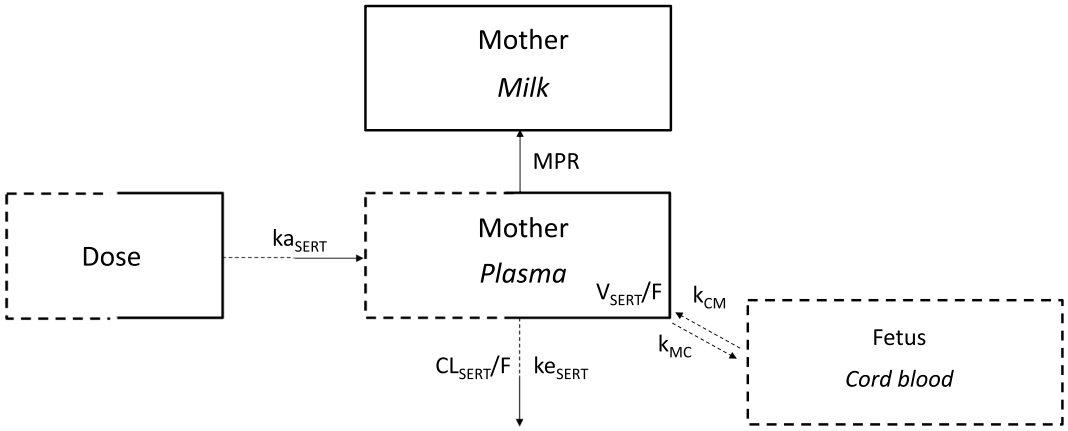

FIGURE 1 Compartmental structure of the final popPK model. Dashed lines represent the pregnancy model and solid lines represent the breastfeeding model. Abbreviations: CL_{SERT}/F, apparent sertraline clearance in maternal plasma; ka_{SERT}, absorption rate; k_{CM}, constant rate from cord blood to maternal plasma; ke_{SERT}, elimination rate; k_{MC}, constant rate from maternal plasma to cord blood; MPR, milk-to-plasma ratio; V_{SERT}/F, apparent sertraline volume of distribution in maternal plasma.

predicted phenotype and CL_{SERT}/F ($\Delta OFV = -4.30$, $P < .05$) when separated into two groups (PM *vs.* IM/NM/UM), not significantly different from a model with four distinct groups. None of the other covariates improved the model fit for CL_{SERT}/F ($\Delta OFV = -3.434$, $P > .05$). MOM ($\Delta OFV = -16.18$, $P < .05$), FEED ($\Delta OFV = -16.11$, $P < .05$), and FAT ($\Delta OFV = -42.95$, $P < .05$) all significantly influenced MPR. Multivariate analyses did not show an independent impact of MOM and FEED in addition to FAT on MPR due to their direct relationship with the fat content in breast milk. The value of MPR increased by 95% when the amount of fat content doubled from 2.59 to 5.18 g 100 mL^{-1}. Moreover, CYP2C19 predicted phenotype on CL_{SERT}/F did not remain a significant covariate ($\Delta OFV = -2.94$, $P > .01$), probably due to the small number of CYP2C19 PM in the studied population. However, because of the clinically significant reduction of CL_{SERT}/F by 42% in CYP2C19 PM compared to other phenotypes, this covariate was retained in the final model together with FAT on MPR. Similar results were obtained with the model including cord blood concentrations. Table 2 presents the final parameter model and the bootstrap results, and Figures S3, S4 and S5 the model goodness-of-fit plots.

3.4 | Model evaluation

The bootstrap results (Table 2) indicate that all parameter estimates from the final model fell within the 95% CI of the bootstrap-generated datasets and were close to the median value (<9%), suggesting a high degree of model stability. Pc-VPC plots (Figure 2) support the good predictive performance of the model.

3.5 | Simulations

Model-based simulations conducted in 10 000 women taking a daily sertraline dose of 50 mg revealed that an exclusively breastfed infant with a daily milk intake of 150 mL kg^{-1} day^{-1} would ingest a median sertraline dose of 6.9 μg kg^{-1} day^{-1} independently of the mothers' CYP2C19 phenotype. The median RID based on these simulations was 0.95%. In terms of ADEQ, an infant would ingest a median cumulative dose of 7.5 mg over 6 months of exclusive breastfeeding, equivalent to a 0.2 standard adult daily dose of sertraline. Importantly, our simulations indicate slightly higher RID and ADEQ values for CYP2C19 PM (1.2% and 0.2 tablets, respectively) than for CYP2C19 non-PM (0.7% and 0.1 tablets). Simulations at maternal daily doses ranging from 25 to 150 mg yielded median infant daily dosages between 3.5 and 20.8 μg kg^{-1} while the median RID remained consistent at 0.95% across the entire dosage range considering both PM and non-PM breastfeeding mothers. For these doses, an exclusively breastfed infant would ingest a median cumulative dose between 2.7 and 28.6 mg, which is equivalent to 0.1–0.6 tablets of 50 mg sertraline. Figure 3 presents simulated RIDs and ADEQs as a function of CYP2C19 phenotypes at all doses, while Table 3 shows median cord blood concentrations and C/P ratios over the entire dosage range. The median predicted cord blood concentrations ranged from 3.29 ng mL^{-1} at a dose of 25 mg to 33.23 ng mL^{-1} at a dose of 150 mg, while the median C/P ratio remained at 0.39 (range 0.14–0.69) for all doses.

4 | DISCUSSION

In this study, we successfully developed a popPK model able to predict infant exposure to sertraline through the placenta and breast milk. The PK parameters CL_{SERT}/F and V_{SERT}/F are consistent with those reported in the general population using noncompartmental analysis, considering the unique context of our pregnant and early postpartum population.[6–8] Indeed, during pregnancy, the volume of distribution and clearance of most drugs are significantly increased, especially towards the end of pregnancy. It may take a few days or weeks for these PK parameters to return to pre-pregnancy values.[46] While three

TABLE 2 PopPK estimates with bootstrap results.

Parameter	Final model Estimates (RSE %)	Bootstrap ($n = 2000$)	
		Median	95% CI
CL_{SERT}/F (L h^{-1}) for CYP2C19 PM	69.6 (19.3)	69.6	47.8–93.4
CL_{SERT}/F (L h^{-1}) for CYP2C19 IM/NM/UM	119 (7)	119.1	104.3–136.3
V_{SERT}/F (L)	2320 (18.4)	2251.5	1503.8–3219.3
k_{aSERT} (h^{-1})	0.315 (26.5)	0.314	0.174–0.623
MPR	1.42 (6.3)	1.42	1.26–1.63
FAT on MPR (%)	93.1 (27.9)	92.3	60.4–114.3
k_{MC} (h^{-1})	0.141 (47.5)	0.135	0.051–0.349
k_{CM} (h^{-1})	0.383 (46.2)	0.367	0.172–0.916
$IIVCL_{SERT}$ (%)	41.5 (15)	40.5	25.2–51.5
σ_{plasma} (%)	37.8 (7.8)	37.4	31.2–43.3
σ_{milk} (%)	42.9 (9.8)	42.2	34.1–49.8
$\sigma_{cord\ blood}$ (%)	30 (13.8)	27.7	16.7–35.9

Abbreviations: CI, confidence interval; CL_{SERT}/F, apparent sertraline clearance in maternal plasma; FAT, fat content in breast milk; $IIVCL_{SERT}$, interindividual variability on CL_{SERT}; IM, intermediate metabolizer; k_{aSERT}, absorption rate; k_{CM}, constant rate from cord blood to maternal plasma; k_{MC}, constant rate from maternal plasma to cord blood; MPR, milk-to-plasma ratio; NM, normal metabolizer; PM, poor metabolizer; RSE, relative standard error; UM, ultrarapid metabolizer; V_{SERT}/F, apparent sertraline volume of distribution in maternal plasma; σ_{plasma}, residual variability.

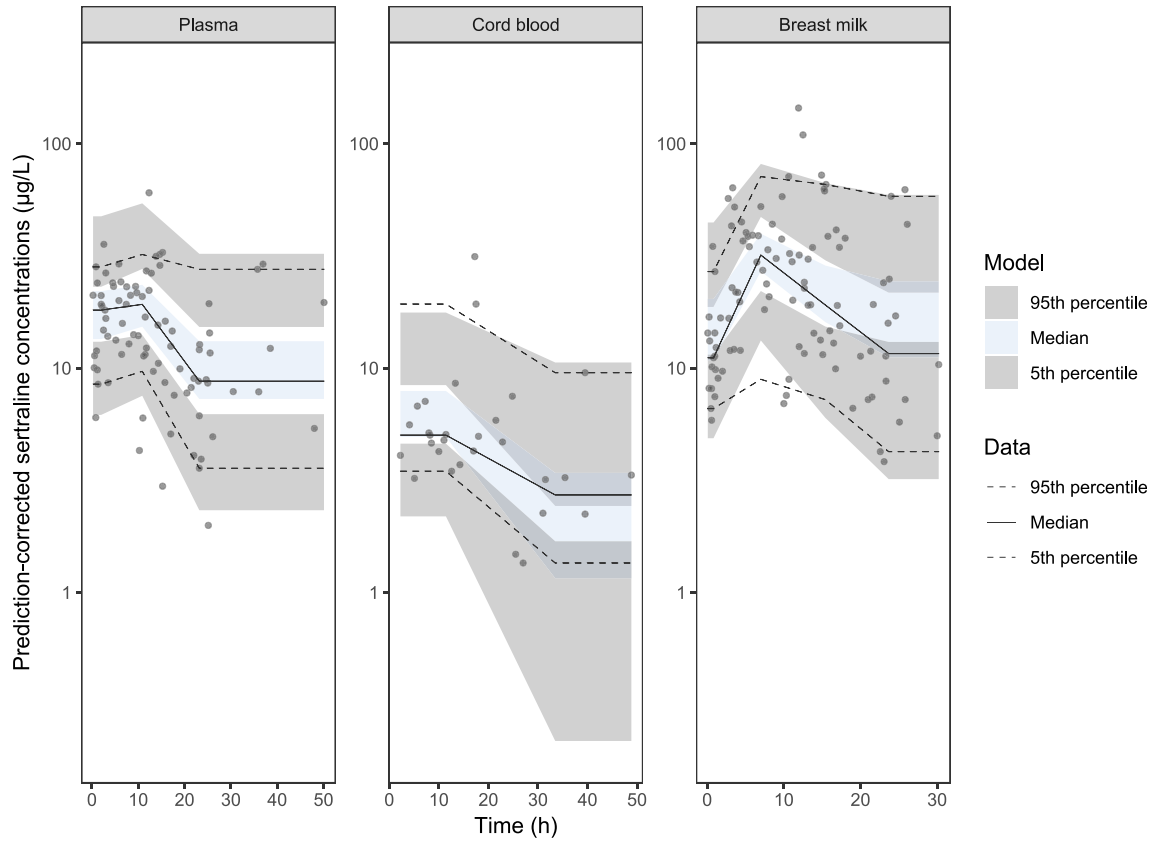

FIGURE 2 Prediction-corrected visual predictive checks of the final covariate model in maternal plasma, cord blood and breast milk. Circles represent prediction-corrected sertraline concentrations, continuous lines and dashed lines represent the population median prediction and the 2.5th and 97.5th percentiles, respectively, and semitransparent grey and blue fields represent the model-based percentile confidence intervals.

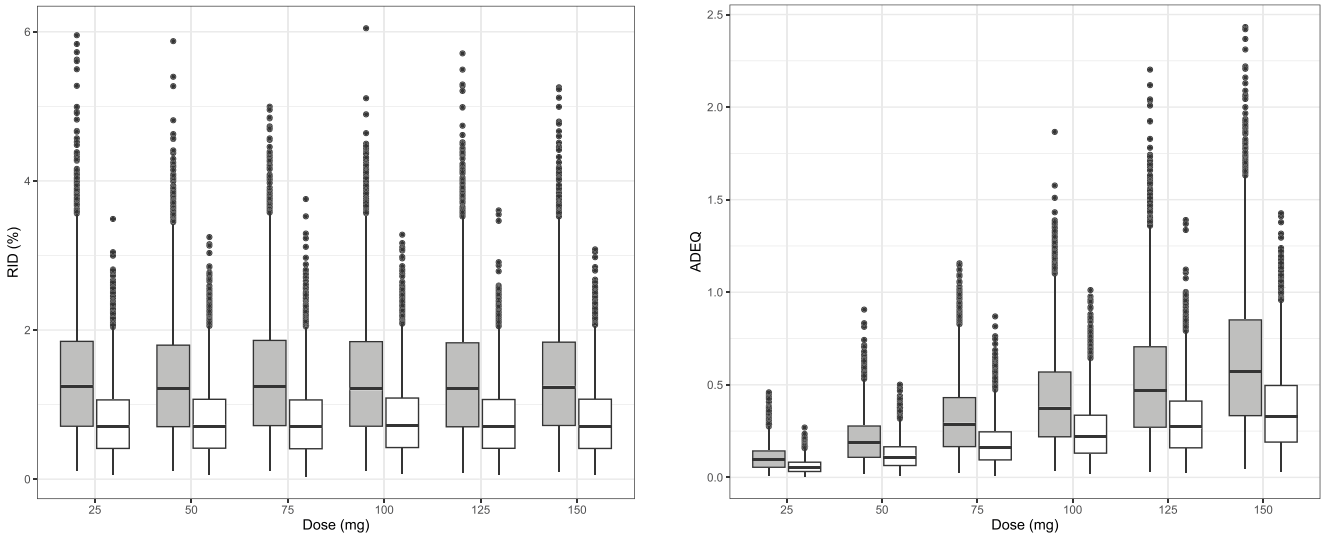

FIGURE 3 RID and ADEQ simulations across the entire dosage range. Grey and white areas represent CYP2C19 PM and IM/NM/UM, respectively. Abbreviations: ADEQ, adult dose equivalent; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RID, relative infant dose; UM, ultrarapid metabolizer.

TABLE 3 Simulated cord blood concentrations and cord-to-maternal plasma (C/P) ratios according to CYP2C19 predicted phenotype at doses between 25 and 150 mg.

	Median cord blood concentration (ng mL^{-1})		Median C/P ratio	
Dose (mg)	CYP2C19 PM	CYP2C19 IM/NM/UM	CYP2C19 PM	CYP2C19 IM/NM/UM
25	5.62	3.29	0.38	0.39
50	11.10	6.65	0.38	0.39
75	16.78	9.90	0.38	0.39
100	22.08	13.17	0.38	0.39
125	27.94	16.45	0.38	0.39
150	33.23	19.70	0.38	0.39

Abbreviations: IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

popPK models for sertraline concentrations in plasma have been published, none of them assessed the transfer of sertraline into the fetus or breast milk.[47–49] Due to the substantial variability in PK parameters obtained in these studies, no direct comparison can be made with our PK parameter estimates. This large variability can be attributed to differences in the populations studied, including age, health status and pregnancy and/or breastfeeding status.

Across the entire dosage range, our results suggest minimal transfer of sertraline into both cord blood and breast milk, thereby resulting in limited exposure of infants to sertraline. This aligns with the high protein binding of the drug.[8] Indeed, our simulations reveal that the median RID remains below 1%, consistently with the literature.[11,16–22] Absolute infant dose and ADEQ results show that 100% of simulated infants at maternal doses of 150 mg day^{-1} would ingest less than 0.13 mg kg^{-1} day^{-1} of sertraline which represents less than three 50 mg tablets over 6 months of exclusive breastfeeding. Moreover, even at high doses of 150 mg day^{-1}, cord blood concentrations would hover around the lower limit of the established therapeutic range of sertraline (10–150 ng mL^{-1}).[8] These findings are reassuring regarding the use of sertraline during late pregnancy and breastfeeding.

Sertraline maternal clearance was significantly lower in mothers identified as CYP2C19 PM compared to other phenotypes, in agreement with existing literature on the impact of CYP2C19 phenotype on sertraline concentrations.[50] Simulations suggested a slightly higher but still limited exposure of infants born to CYP2C19 PM mothers to sertraline through the placenta and breast milk. These results indicate a manageable level of exposure for infants from CYP2C19 PM mothers. Furthermore, the Clinical Pharmacogenomics Implementation Consortium guideline recommends a 50% reduction in sertraline dosage for CYP2C19 PM, which mitigates the potential risk of breastfed infants being exposed to an excessive amount of sertraline.[51] In clinical practice, the CYP2C19 phenotype of mothers is typically unknown prior to sertraline prescription and dose adjustments for breastfeeding women may not be standard practice. Therefore, our results provide reassurance that infants exposed to these doses during this period are unlikely to experience high exposure.

Drug concentrations in breast milk are also influenced by the composition of the milk, and particularly the quantity of fat in the milk. Mature milk and hindmilk contain higher fat content compared to colostrum and foremilk. Thus, lipophilic drugs like sertraline tend to have a greater affinity for mature milk and hindmilk,[16,28] which explains the observed significant association between FAT and MPR in our model. Simulations demonstrated that doubling the FAT from 2.59 to 5.18 g 100 mL^{-1} slightly increased the RID from 0.73% to 1.41%. This minimal increase should have no significant impact on the breastfed infant. Moreover, although of scientific interest, this result lacks clinical relevance, as it is not feasible for a breastfed infant to only ingest foremilk. This result also highlights the critical role of selecting an appropriate experimental design for accurately assessing infant exposure. Indeed, a bias in drug concentration measurements can be introduced, particularly when only samples of foremilk or hindmilk are obtained instead of a well-mixed aliquot.

We acknowledge that our method has certain limitations. Firstly, the number of patients included in the study was limited. A small sample size increases the uncertainty in PK parameter estimates and the risk of being unable to account for the overall IIV. This is likely why we could not estimate the IIV on the MPR, despite some covariates significantly influencing this parameter. Additionally, the small sample size limits our ability to include less common phenotypes. For instance, only two CYP2C19 PM individuals were included in our study, making it challenging to determine the real effect size of this covariate. Future studies with a larger representation of CYP2C19 PM would be beneficial. Similarly, it is possible that we were not able to accurately quantify the true effect of body weight on sertraline exposure, given its significant variation between pregnancy and 4–6 weeks postpartum, due to the presence of multiple missing values. Despite testing numerous covariates in our model, it is possible that other factors such as the mother's feeding state or the use of comedications could explain the remaining unexplained variability. For example, recent studies have demonstrated that the CYP2B6 gene significantly influences sertraline metabolism.[50] Unfortunately, our study did not include screening this gene in women, and its potential role as a covariate should be investigated in future studies. Some information, such as the timing of drug intake prior to sampling, was self-reported by the mothers. This could introduce a memorization bias in the study if the mother does not accurately remember the exact time of drug intake. Finally, we attempted to assess the infant exposure to sertraline during pregnancy and breastfeeding without measuring concentrations in infants to facilitate our study procedures. Consequently, obtained model and estimations do not account for physiological changes and variations that occur during the first months of birth. For instance, CYP2C19 activity in fetuses and newborns before 5 months of age is approximately 12%–15% of the adult activity and CYP2B6 protein is detected in only 64% of samples from birth to 30 days postnatal age.[52,53] Therefore, our simulations may slightly underestimate infant exposure to sertraline. However, this potential underestimation could be balanced by the assumption that all infants are exclusively breastfed with a daily intake of 150 mL kg^{-1} day^{-1} which overestimates the infant's intake and subsequent exposure.[54]

5 | CONCLUSION

Using a popPK approach, we have reaffirmed the limited exposure of infants to sertraline through the placenta and breast milk. This novel popPK model complements existing successful models for drug transfer into breast milk, highlighting the effectiveness of this approach in characterizing the drug PK in cord blood and breast milk, assessing interindividual variability, and identifying the covariates responsible for such variability. Infant exposure to sertraline is influenced by CYP2C19 phenotype and fat content in breast milk but, in any case, remains low and reassuring regarding the use of sertraline during pregnancy and breastfeeding.

AUTHOR CONTRIBUTIONS

Chin B. Eap, Chantal Csajka and Alice Panchaud: Study conception and design; acquisition of data; analysis and interpretation of data; drafting and revising the manuscript for intellectual content. **Nicolas Ansermot, Severine Crettol, Céline J. Fischer Fumeaux, Myriam Bickle Graz, Mathilde Morisod Harari, Etienne Weisskopf, Jean-Michel Hascoët, Olivier Claris and Manuella Epiney:** Acquisition of data; drafting and revising the manuscript for intellectual content. **Anaëlle Monfort, Evelina Cardoso, Peggy Gandia, Karel Allegaert, Pieter Annaert, Hedvig Nordeng, Ema Ferreira, Grégoire Leclair and Monia Guidi:** Analysis and interpretation of data; drafting and revising the manuscript for intellectual content. All authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ACKNOWLEDGEMENTS

The work has been completed as part of the ConcePTION study. The ConcePTION project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 821520. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. The research leading to these results was conducted as part of the ConcePTION consortium. This paper only reflects the personal views of the stated authors. This work was supported by a grant from the Swiss National Science Foundation (SNSF n°320030_135650). The authors want to thank all patients, midwives and nurses involved in this project for their contribution and for providing crucial help in patient recruitment and data collection, especially Mrs Karine Lepigeon (Lausanne University Hospital), Véronique Othenin-Girard (Geneva University Hospital), Sabine Guignon (Maternité Régionale de Nancy) and the Clinical Investigation Center (Hospices Civils de Lyon).

CONFLICT OF INTEREST STATEMENT

The innovative Medicines Initiative is an EU public-private partnership funding health research and innovation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Monfort A, Cardoso E, Eap CB, et al. A population pharmacokinetic model for sertraline in women during the perinatal period—A contribution from the ConcePTION project. *Br J Clin Pharmacol*. 2024;1-12. doi:10.1111/bcp.16177