# Pharmacokinetics and pharmacogenetics of SSRIs during pregnancy: An observational study

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Abstract

*Background*

An involvement of selective serotonin reuptake inhibitors (SSRIs) in increasing the risk of malformations, neonatal withdrawal syndrome, has been suggested recently. Here, we aimed to investigate the contribution of individual pharmacogenetics of SSRI on infants' outcome. We also estimated the umbilical/maternal plasma SSRI concentration ratio in the pregnant women still on SSRI therapy at the time of delivery.

*Methods*

Thirty-four pregnant women, referred to our hospital from January 2011 to July 2015, who were given SSRIs in the third trimester, and related children, were considered. The umbilical/maternal plasma SSRI concentration ratio was estimated in 15 mothers still on SSRI therapy at the time of delivery. For patients with pharmacokinetic analysis, blood samples were collected for pharmacogenetic analyses.

*Results*

Nineteen newborns presented clinical signs possibly related to drug toxicity. A high umbilical/maternal plasma ratio of SSRI was observed in 10 out of the 15 evaluated newborns. Five mothers were intermediate metabolizers and one poor metabolizer for the major CYP enzyme involved in pharmacokinetic pathway.

*Conclusions*

Individualized psychopharmacologic treatment that takes into account mother's exposure to SSRI concentrations and eventually their genetic background may become the standard of care to maximize drug benefit and minimize risks to the newborn.

Key words:        pharmacokinetics, pharmacogenetics, SSRIs, pregnancy

Introduction

Depression is a disorder affecting 7%-15% women in general population [1], 12.7%-18.4% of pregnant women [2] and is a leading cause of disability [3]. Women with severe, chronic, or recurrent syndromes require pharmacotherapy. Selective serotonin reuptake inhibitors (SSRIs) are commonly used antidepressants that act by inhibiting serotonin reuptake in the synaptic cleft. Medications in this group include paroxetine, sertraline, citalopram, escitalopram, and venlafaxine (combined serotonin-norepinephrine reuptake inhibitors). In the past years, SSRIs have been largely prescribed to pregnant women suffering from psychiatric problems, in particular from depression and anxiety. This is based on the assumption that the potential negative effects of untreated psychiatric symptoms from pregnant women largely outweigh the

limited risk for the fetus, especially if the SSRIs are given to women late in the course of the pregnancy [4-6].

Data about infants exposed in uterus to SSRIs are limited due to difficulty in determining exactly when exposure had occurred during pregnancy, the severity of the maternal psychiatric disorder, compliance to therapy, gestational age at exposure, antidepressant dose, comorbidity, and delivery complications. Possible complications following antenatal exposure to antidepressants include adverse pregnancy outcome spontaneous abortion, stillbirth, prematurity, intrauterine growth restriction, neonatal mortality, and, with paroxetine, also teratogenicity [7-9].

Moreover, SSRI intake during pregnancy has also been associated with an increased risk for other neonatal complications such as low birth weight, admission to special care nurseries, persistent pulmonary hypertension [10], and poor neonatal adjustment syndrome (PNAS) [11]. The latter may present as respiratory distress, hypoglycemia, agitation, tremors, irritability, restlessness, jitteriness, low Apgar scores, altered muscle tone, feeding difficulties, and seizures [12]. Among SSRIs, paroxetine and to a significantly lower extent fluoxetine are associated with a slight increase in the risk of fetal malformations, namely cardiovascular ones [2]. Reported incidence of PNAS accounts for up to 30% of newborns exposed to SSRIs and SNRIs [13] from 5% to 85% [14].

Symptoms are generally mild, self-limited, and resolve within a couple of weeks with the notable exception of few cases persisting for months [12-14].

Despite this increased risk of neonatal maladaptation, it seems that SSRI can play a protective role on some deleterious reproductive outcomes, maybe reducing maternal depressive symptoms [15]

In the general population, SSRIs are perceived as wide therapeutic index drug, and therapeutic drug monitoring (TDM) is not routinely performed in the clinical practice. However, according to the recently published AGNP consensus guidelines [16], significant correlations between plasma concentrations of SSRIs and clinical outcome (both efficacy and safety outcomes) have been reported, with most of the molecules having a score level of recommendation of 1 or 2 for the use of TDM. Thus, pregnant women having high SSRI plasma concentrations might be at risk to experience drug-related complications for themselves, and/or to overexpose their fetus to these drugs, increasing also their risk to experience poor perinatal outcome.

Expression of CYP genes, involved in SSRIs hepatic first-pass metabolism, is influenced by a combination of factors including genetic polymorphisms. Distinct CYP pharmacogenetic phenotypes, derived from functional genetic variants, have been associated with the dose requirement, drug efficacy, and occurrence of severe toxicities [17]. Pharmacogenetic guidelines have been published to provide information regarding the interpretation of CYP2C19

and/or CYP2D6 genotype test, to guide SSRI dosing [18]. In the case of CYP2C19, two loss-of-function alleles (*2, *3) create a premature stop codon, whereas *17 results in enhanced gene transcription and an increased metabolic activity [18,19]. For CYP2D6, the major impaired variant alleles are as follows: *3–*6 (non-functional), while CYP2D6 gene duplications and a promoter polymorphism explain a fraction of increased metabolism [19].

The present study aimed at exploring drug-related perinatal complications in newborns from mothers given SSRI during pregnancy and their correlations with estimated umbilical/maternal plasma SSRI concentration ratio, in the pregnant women still on SSRI therapy at the time of delivery, and polymorphisms in genes involved in SSRI metabolism.

Materials and methods

*Patients*

Pregnant patients were recruited between January 2011 and July 2015 from the antenatal clinic of the Luigi Sacco University Hospital (Milano, Italy). Inclusion criteria were as follows: pregnant women treated with SSRI during the third trimester, physiologic pregnancy, no other pharmacologic treatment, and single pregnancy. All patients provided their written informed consent prior to any study procedure. The study was approved by the local ethics committee (Luigi Sacco University Hospital).

*Pharmacokinetic analyses*

Blood samples for the measurement of plasma drug concentrations in the mothers and newborns were collected at delivery. For the newborns, the blood samples were collected from the umbilical cord. After drawing, the collected blood samples were handled on ice; plasma was separated by centrifugation and stored at −20 °C until analysis at the centralized pharmacokinetics laboratory of the pharmacology unit. Plasma concentrations of paroxetine, venlafaxine, sertraline, citalopram, and escitalopram were quantified using liquid chromatography/tandem mass spectrometry methods developed and validated in our laboratory [20]. The lower limit of quantification (LLOQ) of the method was 5 ng/mL for all analytes. The performance of these methods was tested

during each analytical run using internal quality controls, and blinded samples were sent monthly as part of the LCG Standard Proficiency Testing Schemes for Psychoactive Drugs (http://www.lgcpt.com/default.aspx).

Besides absolute plasma concentrations, the umbilical cord/maternal plasma ratio was also estimated for each drug. According to the AGNP guidelines [16], we considered the following ranges of drug concentrations as therapeutic windows: paroxetine, 30-120 ng/mL; venlafaxine (plus the active metabolite), 100-400 ng/mL; sertraline, 10-150 ng/mL; and citalopram, 50-100 ng/mL.


*Genotyping*

Peripheral blood samples were collected from pregnant women who underwent pharmacokinetic analysis. Maternal DNA was isolated using an automatic DNA extraction system (Maxwell® 16 System, Promega, Madison, WI, USA) according to the manufacturer's instructions. Polymorphisms were determined by Real-Time PCR using LightSNiP® (TIB-MolBiol, Berlin) or TaqMan® assay (Thermo Fisher Scientific, Waltham, MA, USA) according the manufacturer's instructions. We evaluated the functional variant mapping in CYP2D6 (*3,*4,*5,*6, rs1080985 promoter variant, gene duplication) for paroxetine, venlafaxine, and citalopram and in CYP2C19 (*2, *3, *17) for sertraline.

*Assessment of newborns' outcome*

Newborns exposed to SSRIs/SNRIs in utero had their vitals assessed at birth and every 4 hours for the first 24 hours including the use of pulse oximetry at each assessment as suggested by the Canadian Guidelines [21]. The first $SpO_2$ was taken at birth if Apgar score was low, otherwise at approximately 1 hour post delivery. Newborns with a low $SpO_2$ or with respiratory distress were treated with $O_2$ supplementation. The diagnosis of PNAS was made after other possible causes of the newborn's symptoms have been ruled out [22]. Symptoms of PNAS (low Apgar score, restlessness, agitation, irritability, lethargy, poor feeding, hypoglycemia, hypothermia, respiratory distress, altered muscle tone, hyperreflexia, jitteriness) were annotated on newborn's medical record until they were resolved. All children were hospitalized for at least 72 hours. Respiratory distress was treated with ventilatory support and/or oxygen supplementation, hypoglycemia with intravenous/oral glucose, and minor symptoms were treated providing supportive care such as a quiet, low-light environment.

Results

*Patient characteristics and clinical outcome*

During the study period, 34 women with reported third trimester exposure to SSRIs and their newborns were included as follows: 11 were treated with paroxetine, 4 with venlafaxine, 15 with sertraline, and 4 with citalopram. Table 1 details the characteristics of the study population and the psychiatric diagnosis of the women at admission.

All mothers were Caucasian and carried a singleton pregnancy. Patients had a medium-low socio-economic status as follows: 20% with a University degree, 25% with a high school diploma, and 55% with a primary school diploma. Approximately 60% of women were married, 40% were living with their own partner and/or family of origin.

Three mothers and three children had some missing data (nd). Pregnant women were at mean age of 36 years (median 35 years). Of about 18 (53%) had a vaginal delivery and 16 (47%) delivered by cesarean section (CS). More in detail, CS was carried out for previous CS (3), maternal choice (4), suspected placental abruption (2), premature rupture of membranes (2), labor dystocia (1), and fetal distress (5).

We evaluated 34 newborns as follows: 17 males (50%) and 17 females (50%). Median gestational age, weight, length, and head circumference were 39 weeks, 3260 grams, 49.5 cm and 34 cm, respectively. These characteristics are in line

with those of the general newborn population [23]. Two newborns were late preterm and four small for gestational age. Nineteen (56%) newborns showed signs or symptoms consistent with PNAS. The most represented symptoms (47%) were the neurological ones including tremors, irritability, hyper-hypotonus, hyperreflexia, jitteriness, and restlessness. Seven newborns had a one-minute low Apgar score (≤7). Respiratory distress requiring oxygen supplementation was present in five newborns, and none manifested pulmonary hypertension or seizures. Seven newborns required admission in the neonatal ward.

*Pharmacokinetics analysis*

Fifteen out of the 34 pregnant women were still on SSRI therapy at the time of delivery, whereas the remaining stopped the drug a few days before partum. Overall, plasma drug concentrations above the LLOQ were detected in all the 15 mothers and 10 newborns (Table 2).

None of the pregnant women treated with citalopram reached therapeutic drug concentrations according to AGNP guidelines (Table 2) [16]. Despite the subtherapeutic citalopram concentrations measured in the pregnant women, the newborns had quantifiable drug concentrations, resulting in higher umbilical/plasma ratios compared with those measured with other SSRIs. Worthy of mention, in one out of the three newborns, the concentrations of

citalopram were higher compared with those measured in the mother, resulting in an umbilical/plasma ratio of 141.6%. No trend for association between citalopram pharmacokinetics and newborns' outcome was observed. Subtherapeutic exposure was also observed in the two pregnant women given paroxetine (Table 2). Conversely, the only pregnant woman given venlafaxine had drug plasma concentrations in the therapeutic range. Interestingly, in the corresponding newborn, we measured a venlafaxine concentration of 78.9 ng/mL, a value close to 100 ng/mL, considered as the minimum therapeutic concentration in adults. In this case, we also observed an umbilical/plasma ratio of 39.5%.

As shown in Table 2, 50% of the pregnant women given sertraline had therapeutic drug concentrations at the time of delivery, with umbilical/plasma ratios ranging from 23.9% to 102.4%.


*Pharmacogenetic analysis*

Overall, variant alleles in CYP2C19 and CYP2D6 genes were detected in 8 out of 15 mothers.

More in detail, CYP2C19 gain- and loss-of-function alleles were found in four mothers and CYP2D6 loss-of-function alleles in two mothers (Table 2).

Paroxetine is extensively metabolized by CYP2D6 to compounds with little pharmacological activity toward serotonin reuptake inhibition. Variations in

CYP2D6 activity may result in lower or greater exposure to these drugs. For an individual with CYP2D6 reduced activity, the guideline recommended an alternative drug not predominantly metabolized by CYP2D6 or, if a paroxetine use is warranted, a 50% dose reduction. Interestingly, a mother ID1 with a CYP2D6 deletion in heterozygous (*5) showed higher paroxetine levels, and her child presented a more severe adverse outcome (Table 2).

The major metabolic pathway for sertraline is CYP2C19, and the enzyme activity variation may result in altered drug exposure. Interestingly, a newborn ID25 presented severe adverse events, and her mother carried two loss-of-function alleles of CYP2C19 (*2/*2) (Table 2).

Citalopram and its N-demethylated metabolites exist as racemic compounds. In vitro and in vivo tests showed that the effects of citalopram and N-demethylcitalopram are mainly or solely due to the S-enantiomers. The formation of R/S-demethylcitalopram is catalyzed mainly by the isoenzymes CYP2C19. Defective maternal alleles were detected in ID24 (Table 2).

Discussion

The use of SSRI during pregnancy has been increasing, currently occurring in up to 2%-6% of pregnant women [6]. Mothers taking SSRI are more likely to be older, having undergone cesarean section more frequently than the general population. Intrauterine exposure may lead to neonatal symptoms especially from the central nervous system; PNAS is the most frequently reported one. How an exposure to SSRIs leads to PNAS is still unknown. PNAS could be the consequence of abstinence due to the discontinued distribution of the pharmacological substance at delivery as well as to serotonergic overstimulation or genetic predisposition.

A lot has been, indeed, written on the use of SSRI during pregnancy and possible short- and long-term negative outcomes on neonates [3-10]. We know that different degrees of outcomes are possible, and not all the newborns exposed to SSRIs during pregnancy definitely will develop a negative outcome. For this reason it is not possible to casually establish whether the adverse outcome of infants in utero exposed to SSRIs is worse than in a general population. However, a recent study has shown that the profile of neurobehavioral development was different for SSRI-exposed versus non-exposed infants [24]. So far, still little is known about the possible etiologic mechanism that could not only explain the adverse neonatal effects but also the degree of clinical involvement and presentation in the early period after birth.

On this regard, pharmacokinetics and pharmacogenetics might potentially explain a part of the observed variability in the clinical neonatal outcome after in utero exposure to SSRIs (reviewed in [25]).

Fifty-six percent of newborns in our study presented one or more symptoms consistent with PNAS. Seven out of 34 infants required admission to the neonatal ward mainly for respiratory distress syndrome or neurologic disorders. Interestingly, for each drug, the worst adverse outcome was observed in infants born to the mothers with the high umbilical/maternal plasma ratio of SSRI and altered CYP activity as emerging from the pharmacogenetic analysis. More in detail, case ID1, whose mother had a CYP2D6 gene deletion (*5), presented a low one-minute Apgar score, respiratory distress, bradycardia, hypotonia, and hyporeflexia and needed resuscitation efforts and ventilatory support during the first 18 hours of life; the patient also showed hypoglycemia and episodic phasic contraction of all limb miming seizures, EEG and cerebral ultrasound were normal. Postural muscle response onset latencies were significantly shorter than the responses found in age-matched normal children, later she presented the reduction of isolated arm and leg movements, increased unilateral tendon reflex. These symptoms resolved in two months. Interestingly, this case showed the highest maternal plasma paroxetine concentration. Taken together, the PK/PG characteristics allowed us to speculate that the observed adverse outcome may

be reasonably explained by a decreased metabolism of the paroxetine into the mother.

Another interesting case, ID25, presented a mild respiratory distress at birth, self-limited by 3 hours, accompanied by jitteriness and tremors that lasted 48 hours. Generalized hypotonia resolved at one month of life. Interestingly, her mother carries two loss-of-function alleles of CYP2C19 (*2/*2), which are consistent with a poor metabolizers phenotype, and therefore reduced clearance of sertraline. This is indirectly supported also by a high sertraline umbilical/maternal plasma ratio.

A very interesting case, at least from a pharmacokinetic viewpoint, is mother ID16, being characterized by the highest plasma drug concentrations, highest exposure measured in the plasma newborn, with concentrations that approximate those considered as therapeutic in adults [16] and poor neonatal outcome (prematurity, low Apgar Score needing neonatal resuscitation).

Even if PNAS is self-limiting and transient, newborns of SSRI treated mother should be monitored in the first few days of life. Management of PNAS primarily consists of supportive care. Identification of infants at risk of PNAS—because of the severity of maternal psychiatric illness, maternal age, cesarean section, prematurity, or low birth weight—is critical to child management since it could significantly influence the neonatal outcomes.

Several limitations do exist in our preliminary observations, such as the presence of potential confounders, as the difficulty to determine exactly when the exposure to SSRIs occurred. Moreover, a significant percentage of mothers withdrew SSRIs a few days before delivery, a condition that did preclude a complete analysis of potential correlations between clinical outcome, TDM, and pharmacogenetic results. Furthermore, with regard to the pharmacogenetic aspect, we only took into account the maternal genetic background and the major genetic variants that affect the expression and activity of the CYP enzymes. Finally, the possibility that other non-genetic, non-pharmacokinetic factors may have affected the outcome of the studied newborns cannot be definitively ruled out.

*Conclusions*

Our preliminary observation suggests that genetic polymorphisms that affect SSRI metabolism may play a role, together with other clinical covariates, in the development of PNAS. Despite the observational design, we are confident that our hypothesis/generating investigation may provide the rationale for the design of a large, adequately powered, prospective study aimed at formally investigating the contribution of pharmacokinetics/pharmacogenetics on the outcome of pregnant women given SSRIs.

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**Table 1. Characteristics of study population**

|  | Pregnant women (n = 34) |
|---|---|
| Age (years) | 34.6±4.5 |
| BMI before pregnancy (kg/m$^2$) | 24.2±4.6 |
| BMI at delivery (kg/m$^2$) | 29.1±4.9 |
| Smoking (any quantity) | 13 (38%) |
| Primiparity | 11 (32%) |
| Major Depressive Disorder | 12 (35%) |
| Anxiety Disorder (mainly Panic Disorder) | 6 (18%) |
| Mixed Anxiety-Depressive Disorder | 15 (44%) |
| Other diagnosis | 1 (3%) |

Data are presented as mean ± standard deviation or absolute number (%)

**Table 2. Individual pharmacokinetic, pharmacogenetic data and infant's adverse outcome**

| SSRI | Patient ID | Drug dose (mg/day) | Mother's [drug] (ng/mL) | Infant's [drug] (ng/mL) | Umbilical/ Maternal ratio (%) | Major CYP metabolizers | Mother's genotypes | *Expected phenotype* | #Infant's adverse outcome immediately after delivery (later events in brackets) |
|---|---|---|---|---|---|---|---|---|---|
| Paroxetine | 1 | 20 | 48.6 | 10.3 | 21.2 | CYP2D6 | *1/*5 | IM | Prematurity, low Apgar score, RDS, neurologic symptoms |
| | 32 | 25 | 23.4 | 9.1 | 38.9 | | *1/*4 | IM | None (acrocyanosis at 8 hours of life) |
| | | | | | | | | | |
| Venlafaxine | 16 | 150 | 199.8 | 78.9 | 39.5 | CYP2D6 | *1/*1 | EM | Prematurity, low Apgar score |
| | | | | | | | | | |
| Sertraline | 27 | 75 | 89.0 | 35.5 | 39.9 | CYP2C19 | *1/*1 | EM | None (tremors at 24 hours of life) |
| | 22 | 100 | 32.7 | 7.8 | 23.9 | | *2/*17 | IM | None (poor feeding) |
| | 30 | 75 | 25.3 | <5 | | | *1/*1 | EM | SGA |
| | 25 | 50 | 24.5 | 11.1 | 45.3 | | *2/*2 | PM | RDS, neurologic symptoms |
| | 14 | 75 | 12.7 | 13.0 | 102.4 | | *2/*17 | IM | None |
| | 15 | 25 | 9.5 | <5 | | | *1/*1 | EM | None |
| | 28 | 75 | 9.4 | <5 | | | *1/*17 | UM | SGA |
| | 29 | 75 | 9.4 | <5 | | | *1/*17 | UM | None |
| | 23 | 50 | 9.2 | 6.5 | 70.7 | | *1/*1 | EM | SGA |
| | 10 | 50 | 7.4 | <5 | | | *1/*1 | EM | Low Apgar score |
| | | | | | | | | | |
| Citalopram | 11 | 5 | 10.1 | 14.3 | 141.6 | CYP2C19 | *1/*1 | EM | None |
| | 24 | 10 | 9.3 | 5.5 | 54.3 | | *1/*2 | IM | Neurologic symptoms |

Patients are listed in order of decreasing values of mother's concentration for each drug.

*Expected genotype defined according pharmgkb guideline (www.pharmgkb.org): Extensive Metabolizer (EM), Intermediate Metabolizer (IM), Poor Metabolizer (PM).

#SGA: small gestational age; RDS: respiratory distress syndrome