CORRELATION BETWEEN PHARMACOKINETICS AND PHARMACOGENETICS OF SSRIs/ SRNIs AND MATERNAL AND NEONATAL OUTCOMES: RESULTS FROM A NATURALISTIC STUDY IN PATIENTS WITH AFFECTIVE DISORDERS

Running Head: SSRIs/SNRIs and maternal and neonatal outcomes

Key-words: Pharmacokinetics, Pharmacogenetics, SSRIs/SNRIs, Pregnancy, Affective Disorders, postpartum complications.

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the data that support the findings of this study are available from the corresponding author upon reasonable request.

ABSTRACT

OBJECTIVE: Some studies linked the use of Selective Serotonin Reuptake Inhibitors and Selective Serotonin and Noradrenaline Reuptake Inhibitors (SSRIs/SNRIs) to the risk of perinatal complications.

This study explored the relationship between pharmacokinetics and pharmacogenetics, SSRIs/SNRIs tolerability and effectiveness and maternal and newborn outcomes.

METHODS: 55 pregnant women with DSM-5 diagnoses of affective disorders, treated with SSRIs/SNRIs, were recruited and, during the third trimester, their blood samples were collected for pharmacokinetics and pharmacogenetics analyses. Plasma levels and metabolic phenotypes were then related to different obstetrical and maternal outcomes.

RESULTS: The pharmacokinetic data were more stable for Sertraline, Citalopram and Escitalopram compared to other molecules (p=.009). The occurrence of Postnatal Adaptation Syndrome (PANS) onset was associated with higher plasma levels for Sertraline (median at delivery: 16.7 vs 10.5 ng/mL), but not for Fluoxetine and Venlafaxine. Finally, the subgroup with in range plasma concentrations had less blood losses than the below range subgroup (p=.030).

CONCLUSIONS: Plasma levels of Sertraline, Citalopram and Escitalopram were more frequently in range in late pregnancy when compared to other drugs. The drugs plasma concentrations in range do not strictly correlated with worse perinatal outcomes

compared with below range plasma concentrations, with possible differences between the different drugs.

Introduction

The prevalence of Antenatal Depression is estimated to affect about 15% of all pregnant women (Okagbue et al., 2019). Period prevalence estimates show that almost 20% of women have depressive symptoms during the first three months postpartum, with approximately 7.1 % having a major depressive episode during this period (Gavin et al., 2005). The pooled prevalence of anxiety disorders during pregnancy is 3%, and up to 6% for specific phobia, while the prevalence of obsessive compulsive disorder (OCD) is around 3%. In addition up to 14.4% of women may develop specific anxiety symptoms related to pregnancy condition, birth and maternity (Poikkeus et al., 2006).

Regarding the use of antidepressants during pregnancy, most studies and meta-analyses consider the risk of major malformations linked to the use of SSRIs/SNRIs not significant (Gao et al., 2018). However, for SNRIs, significantly less data are available (Lassen, Ennis, & Damkier, 2016). In particular, the cardiac malformations are those more frequently reported (Biffi et al., 2020; Grigoriadis, VonderPorten, Mamisashvili, Roerecke, et al., 2013). Some studies linked the SSRIs/SNRIs use to an increased risk of spontaneous abortion (Steinberg et al., 2018), preeclampsia (PE) (Palmsten et al., 2020), postpartum hemorrhages (PPH) (Palmsten et al., 2020), postnatal adaptation syndrome (PNAS) (Grigoriadis, VonderPorten, Mamisashvili, Eady, et al., 2013), low birth weight

(LBW) lower APGAR scores (Biffi et al., 2020) and persistent pulmonary hypertension (PPHN) (Ng et al., 2019) . These complications are similar to those reported by patients with depressive and anxiety disorders during pregnancy (Khanghah, Khalesi, & Hassanzadeh, 2020; Vivenzio, Nardi, & Bellantuono, 2018), except for PPHN (Ng et al., 2019) and PNAS (Grigoriadis, VonderPorten, Mamisashvili, Eady, et al., 2013) which are more specifically related to antidepressant exposure in late pregnancy.

Physiological changes, such as increased volume of distribution, reduced albumin concentration, modulation of metabolic enzymes by pregnancy hormones and increased renal drug clearance, influence the plasma level of antidepressants in mothers and the amount transferred to the fetus (Abduljalil, Furness, Johnson, Rostami-Hodjegan, & Soltani, 2012; Isoherranen & Thummel, 2013). Therefore, therapeutic drug monitoring (TDM) is recommended to guide therapy (Deligiannidis, Byatt, & Freeman, 2014).

Based on the above, the aim of our study was to evaluate the possible correlation between pharmacokinetics and pharmacogenetics analyses and perinatal outcomes, concomitant use of SSRI/SNRIs during pregnancy, in order to promote individualized treatment of affective and anxiety disorders in pregnant women.

Materials and methods

Enrolled Patients

Fifty-five women, enrolled between 2011 and 2018 at the Depressive Disorders Treatment Centre of the Department of Psychiatry and at the Department of Gynecology and Obstetrics of the ASST Fatebenefratelli–Sacco University Hospital (Milano, Italy), received treatment with Sertraline, Paroxetine, Citalopram, Escitalopram, Fluoxetine or Venlafaxine ER by their own prescribing physician. All women were taking

antidepressants before pregnancy, were followed in our Clinic and carried out monthly psychiatric visits during pregnancy. Any dose changes were based on clinical evaluation. All women underwent second level obstetrical-gynecological visits.

Gynecological maternal outcomes were obtained through periodic medical reports and discharge letters. Also, the outcomes of newborns exposed to SSRIs and SNRIs in utero were obtained through newborns discharge letters and by periodic medical reports.

The local Ethics Committee had previously approved the study protocol. All patients provided a written informed consent before undergoing any study procedure.

Inclusion criteria comprised diagnosis of depressive and/or anxiety disorder according to DSM-5 criteria and an ongoing treatment with SSRIs/SNRIs during pregnancy.

Exclusion criteria were represented by any of other concomitant psychopharmacological therapy with the exception of benzodiazepines up to an equivalent dose of 0.5/day mg of Alprazolam.

Pharmacokinetic Analyses

Maternal blood samples were obtained from venous samples, collected by the mother in the third trimester of pregnancy from the 26th week of gestation onwards. Blood samples for plasma dosages were taken approximately 12 hours after the last SSRI/SNRI administration. Plasma was separated by centrifugation and stored at -20°C until analysis. Plasma concentrations of Paroxetine, Fluoxetine, Sertraline, Citalopram, Escitalopram and Venlafaxine were quantified using liquid chromatography/tandem mass spectrometry methods developed and validated in the centralized pharmacokinetics laboratory of the pharmacology unit (Baldelli, Fucile, & Cattaneo, 2011). The lower limit of quantification 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 LGC Standard Proficiency Testing Schemes for Psychoactive Drugs (http://www.lgcpt.com/default.aspx). According to the AGNP guidelines (Hiemke et al., 2018), we considered the following ranges of drug concentrations as therapeutic ranges: Paroxetine, 20-120 ng/mL; Fluoxetine, 120-500 ng/mL; Sertraline, 10–150 ng/mL; Citalopram, 50–110 ng/mL; Escitalopram, 15–80 ng/mL; and Venlafaxine (plus the active metabolite), 100–400 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) according to the manufacturer's instructions. The presence of polymorphisms was determined by Real-Time PCR, using LightSNiP (TIB-MolBiol, Berlin) or TaqMan assay (Thermo Fisher Scientific, Waltham, MA) according to the manufacturer's instructions. We evaluated the functional variant mapping in CYP2D6 (*3,*4,*5,*6, rs1080985 promoter variant, gene duplication) for Paroxetine, Venlafaxine, Fluoxetine, in CYP2C19 (*2, *3, *17) for Sertraline, Escitalopram and Citalopram.

Statistical analysis

Firstly, we conducted a descriptive analysis of the socio-demographic features of the sample. In particular, median for continuous variables and frequencies and percentage for qualitative variables were performed. Then, Mann-Whitney test and Chi-square test were used to compare qualitative and quantitative variables respectively. The

significance threshold was considered $p<.05$. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 24.

Results

Table1 summarizes the socio demographic characteristics of the total sample, psychiatric diagnosis and treatment.

Pharmacokinetics

Table2 for each woman, summarize pharmacokinetic, pharmacogenetic data and maternal/neonatal outcomes.

The administered antidepressants were the following: Sertraline in 24 patients (43.6%), daily dose between 50 and 150 mg; Paroxetine in 11 patients (20%), daily dose between 10 and 40 mg; Fluoxetine in 4 patients (7.3%), daily dose between 20 and 30 mg; Escitalopram in 7 patients (12.7%), daily dose between 5 and 10 mg; Citalopram in 2 patients (3.6%), daily dose of 20 mg; Venlafaxine ER in 7 patients (12.7%), daily dose between 37.5 and 150 mg.

The medians of the daily drug doses for each antidepressant at third trimester were the following: 75 mg for Sertraline; 20 mg for Paroxetine; 25 mg for Fluoxetine; 20 mg for Citalopram; 10 mg for Escitalopram; 75 mg for Venlafaxine ER. The medians of the plasma levels at third trimester of each drug were the following: 15.5 ng/mL for Sertraline; 6.4 ng/mL for Paroxetine; 346.8 ng/mL for Fluoxetine (of which only one

value was available); 52.5 ng/mL for Citalopram; 12.1 ng/mL for Escitalopram; 86.1 ng/mL for Venlafaxine ER.

Considering plasma levels available at third trimester for each drug, the following patients had plasma drug concentrations in range: 11 (91.7%) on Sertraline; 2 (33.3%) on Venlafaxine ER; 1 (25%) on Paroxetine; 1 (50%) on Citalopram; 2 (50%) on Escitalopram; for Fluoxetine, only one data was available and it was in the therapeutic range. Plasma concentrations of the following women were undetectable (<5 ng/mL): 1 for Sertraline, 2 for Paroxetine and 2 for Escitalopram.

In our sample, the plasma levels of Sertraline, Citalopram and Escitalopram (mainly metabolised by CYP2C19) (Hicks et al., 2015) were more frequently in the therapeutic range (p=.046) compared with Paroxetine, Venlafaxine ER and Fluoxetine (mainly metabolised by CYP2D6) (Hicks et al., 2015; Sangkuhl, Stingl, Turpeinen, Altman, & Klein, 2014; Blazquez, Mas, Plana, Lafuente, & Lázaro, 2012). This result was more consistent considering the extensive metabolizers (EM) and untrarapid-rapid metabolizers (U-RM) alone (p=.009).

For 30 mother-child couples the umbilical/maternal ratio was available. This percentage value of umbilical plasma concentrations relative to those of the mother (table 2). The median umbilical/maternal ratio was 21.2% for Paroxetine, 39.9% for Sertraline, 59.1 for Citalopram for which one data was available, 67.8% for Escitalopram, 76.8% for Fluoxetine and 130.5% for Venlafaxine ER.

Pharmacogenetics

It was possible to perform pharmacogenetic analysis for 42 patients (76.4 % of the total sample).

To make the data comparable, we divided the plasma concentration (in ng/mL) by the oral dose (in mg/day), resulting in a concentration-by-dose ratio (C/D) (Reis et al., 2004). For each drug, we calculated the C/D median and comparing the medians of the poor (PM) and intermediate (IM) vs extensive (EM) and ultra-rapid metabolizers (U-RM), observing the following values: Sertraline 0.31 (IM+PM) vs 0.26 (U-RM+EM); Paroxetine: 2.56 (IM+PM) vs 0.37 (EM); Escitalopram: 3.63 (IM) vs 0.63 (EM); Venlafaxine ER: only one I/EM with the C/D value of 2.06, the median C/D of EM was 1.15; Of the 2 patients on Citalopram, 1 EM with the C/D value of 4.51 and 1 IM with the C/D value of 0.74. Considering drug plasma levels at third trimester, 8 patients (61.5%) in the U-RM and EM subgroup had below-range plasma levels, while only 2 (20%) patients in the PM and IM subgroup had below-range plasma levels. The different drug plasma concentrations based on the metabolic phenotype were shown in figure 1.

Considering drug interactions, we observed the following cases, we considered the drugs most involved in the possible interactions: ID13 taking Sertraline 75 mg/day (plasma concentration: 26 ng/mL) and Phenobarbital, ID18 taking Sertraline 100 mg/day (plasma concentration: 12,1 ng/mL) and antiretrovirals. Drug Plasma concentrations of all patients were in therapeutic range, despite the metabolic phenotype and type of polytherapy.

Neonatal and maternal outcomes

In terms of neonatal outcomes, 10 (18.2%) newborns were SGA; 5 (9.1%) newborns were born preterm; 8 (14.5%) newborns had a one-minute low Apgar score <7; 1 (1.8%) newborn had a five-minute low Apgar score <7 and was born to a woman who took Sertraline and antiretrovirals; 14 (25.4%) newborns showed signs or symptoms belonging to PNAS. Considering PNAS, the mothers of these newborns were taking the following

drugs: 7 on Sertraline, 3 on Paroxetine, 2 on Escitalopram, 1 on Citalopram, 1 on Venlafaxine ER and no infants whose mothers took fluoxetine developed signs of PNAS. Considering the largest subsample of women on Sertraline, it was found that median plasma concentrations at third trimester and delivery were higher in patients whose newborns developed symptoms of PNAS, though not statistically significant (median plasma level at third trimester: 19.5 ng/mL vs 14.1 ng/mL; median plasma level at delivery: 16.7 ng/mL vs 10.5 ng/mL). Indeed, PNAS was not associated with serious long-term complications and spontaneously resolved within 24 hours after adequate monitoring or transient oxygen supplementation. One newborn needed to be transferred to Neonatal Intensive Care Unit (NICU): the mother was taking Sertraline (daily dose 100 mg, plasma concentration: 12.1 ng/mL) and antiretrovirals.

Malformations were reported in 4 newborns: 2 (3.6%) cases of congenital clubfoot, 1 (1.8%) case of bicuspid aortic valve, 1 (1.8%) case of toe polydactyly. No case of major malformations was reported.

Pregnancy complications were the following: 11 (20%) patients reported premature rupture of membranes (PROM), 3 (5.4%) patients suffered from gestational diabetes mellitus (GDM), 9 (16.4%) patients reported PPH (defined as blood loss > 500 cc in vaginal delivery and > 1000 cc in caesarean section, according to the definition of the ICD 10), 1 (1.8%) patient had preeclampsia. Considering the 53 women with blood loss values available, it was found that the subgroup with drug plasma concentrations in therapeutic range at delivery (or third trimester when dosage at delivery was not available) had a significantly lower mean blood loss than the subgroup with concentrations plasma levels below therapeutic range ($p = .030$). The difference in blood loss between the two subgroups was confirmed in case of vaginal delivery ($p = .020$), while no significant difference was observed in case of caesarean section ($p = .257$). This

result confirms a previous result from a sample of 43 women whose plasma concentration was available at delivery (Perrotta et al., 2019).

Discussion

In our study, the slower genotypes (poor and intermediate metabolizers) showed higher plasma concentrations (Figure 1). On the other hand, the extensive and ultra-rapid metabolizers treated with Paroxetine, Fluoxetine and Venlafaxine (metabolised primarily by CYP2D6) (Blazquez et al., 2012; Hicks et al., 2015; Sangkuhl, Stingl, Turpeinen, Altman, & Klein, 2014) showed lower plasma concentrations and, not infrequently, below the therapeutic range. These results might be explained by pregnancy induced increase in CYP2D6 metabolism and related effects on specific genotypes, suggesting that ultra-rapid and extensive metabolizers exhibit lower plasma concentrations than slower genotypes (Koren & Ornoy, 2018). Therefore, some drugs may necessitate a dose increase during the third trimester of pregnancy in order to maintain the therapeutic efficacy (Westin, Brekke, Molden, Skogvoll, & Spigset, 2017).

The plasma concentrations of Sertraline, Citalopram and Escitalopram as a whole were significantly more frequently in range than other drugs (p=.046). Though limited studies have been conducted in this regard, the effect of pregnancy on CYP2C19 inhibition might play a crucial role (Westin et al., 2017). In this perspective, the greater stability of therapeutic plasma concentrations may require fewer dose adjustments in order to maintain therapeutic efficacy. Our results were also more confirmed by considering EM alone (p=.009). Indeed, IM and PM have been associated with higher plasma concentrations, as shown by general population data (not pregnant population) (Hicks et al., 2015). The identification of poor metabolizers could have clinical implications including to avoid the risk of overdose (Hicks et al., 2015). Ultimately, these findings

need confirmation on larger samples. Furthermore, though not certainly, it is not possible to exclude a drug interruption for those patients with plasma concentrations <5 ng/mL.

Malformations occurred in 4 cases (less than 4% of the total sample). The teratogenicity risk is primarily related to first trimester exposure (not investigated in our study), but data about placental passage in the first trimester are lacking (Lusskin et al., 2018) and it is difficult to demonstrate a direct cause-effect correlation between drugs and malformations. The plasma level at early pregnancy could be considered in future studies.

Our data suggest a possible correlation between plasma levels in late pregnancy and the occurrence of PNAS. Higher plasma concentrations of Sertraline in both mothers and infants at delivery for infants with PNAS symptoms seem to suggest withdrawal aetiology. Indeed, the small size of the subgroups did not allow evaluations for other drugs. However, considering the umbilical ratios, the values were higher for Venlafaxine and Fluoxetine when compared with Sertraline. Unexpectedly, no newborns whose mothers were taking Fluoxetine and only one preterm infant whose mother was taking Venlafaxine ER (Hogue et al., 2017), developed PNAS. Apparently, this is in contradiction withs the previous data for Sertraline, but it could be explained as follows: the long half-life of Fluoxetine and its metabolite can, at least theoretically, decrease the risk of PNAS as the plasma concentration is reduced more gradually (McLean, Murphy, Dalfen, & Shea, 2019). The slow-release formulation Venlafaxine might partially promote the same effect, reducing the peak plasma concentration, but the small size of our sample does not allow definitive conclusions. Some studies have reported neonatal Venlafaxine discontinuation syndrome, but the results are insufficient and further studies are needed in this field (Holland & Brown, 2017) (Holland J. et al., 2016).

The clinical indication of a temporary drug dose decrease about two weeks before delivery (Goracci, Valdagno, Maltinti, Sillari, & Fagiolini, 2015) must be balanced with an assessment of the clinical status and the risks of relapse in postpartum. Moreover, further studies are needed to better evaluate possible differences between each drug and etiopathogenesis (withdrawal or toxicity) of the multiple syndromic symptoms (Nordeng & Spigset, 2005).

Our results showed significantly lower blood values in women with in range vs below range plasma concentrations. The small size of the total sample and sub-group in relation to drugs, as well as the possible presence of confounding factors, do not allow definitive conclusions. Literature regarding the correlation between the use of SSRIs and postpartum hemorrhage shows conflicting data (Bruning et al., 2015; Heller et al., 2017; Kim et al., 2016; Skalkidou et al., 2020). These drugs, reducing the concentration of serotonin in platelets, through the SERT blockade operated by the SSRIs and SNRIs, increase serotonin plasma level (C., S., K.B., & K.S., 2010; Saldanha, Kumar, Ryali, Srivastava, & Pawar, 2009) and this could increase the tonicity of the uterus and, therefore, its ability to limit blood loss (Cordeaux, Pasupathy, Bacon, Charnock-Jones, & Smith, 2009). Some studies on histological samples of myometrium obtained at the time of birth revealed that the activation of the 5HT2A serotonergic receptors, expressed by muscle cells, causes its sustained contraction (Cordeaux et al., 2009; Grzeskowiak, McBain, Dekker, & Clifton, 2016; Hanley, Smolina, Mintzes, Oberlander, & Morgan, 2016; Joseph et al., 2015; Kim et al., 2016; Lindqvist, Nasiell, Gustafsson, & Nordstrom, 2014; Lupattelli, Spigset, Koren, & Nordeng, 2014; Palmsten et al., 2013; Salkeld, Ferris, & Juurlink, 2008). In this regard, our result does not seem to totally exclude a possible protective role, described in the literature, but deserve additional investigation.

Of note, one patient (ID 6) was taking Venlafaxine ER (daily dose 37.5 mg, plasma concentration 37,6 ng/mL) and presented Gestational Hypertension and PE in addition to

GDM, PTB and a malformation in her newborn. Venlafaxine is known to be associated with a risk of dose-dependent increases in blood pressure (Thase, 1998), but few studies conducted in pregnant women are available in this respect (Newport et al., 2016; Zakiyah et al., 2018). Given the potentially dangerous consequences of hypertension related to pregnancy (as exemplified by our outpatient) further studies were needed in this field.

Finally, the patients taking polytherapy had the plasma concentrations in the therapeutic range.

This could be related to the treatment with Sertraline and Escitalopram administered to them. Indeed, Sertraline and Escitalopram showed lower risk of drug-drug interaction than some other antidepressants (Caballero & Nahata, 2005). Moreover, some women were treated with antiretrovirals (inhibitor of CYP3A4 and CYP2D6) (Gong et al., 2019), phenobarbital (inducer of CYP3A4 and low inhibitor of CYP2D6) (He, Chen, Zhou, & Zhou, 2015). Those drugs could be involved in drug-drug interactions. The administration of other drugs in polytherapy could be considered when an antidepressant must be introduced during pregnancy, choosing the compounds with a lower risk of interactions and consequently possible changes in related plasma concentrations and efficacy. If patients need to continue antidepressants with increased risk of interactions, TDM represents an important tool for both antidepressants and other drugs, especially antiretrovirals and antiepileptics (Gong et al., 2019).

Given the complexity of physiological changes induced by pregnancy variable, individual genotype and potential intra SSRIs/SNRIs classes pharmacokinetic differences, though preliminary, our data show the importance of pharmacogenetic and pharmacokinetic analyzes to support a correct evaluation and interpretation of the perinatal outcomes and their validity to orient clinical practice, in order to improve the personalization and

safety of the perinatal treatment of affective disorders, in order to increase a precision medicine approach.

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Table 1 Socio-demographic, clinical features of total sample. MDD=Major Depressive Disorder; GAD=Generalized Anxiety Disorder; OCD=Obsessive Compulsive Disorder; BN=Bulimia Nervosa

Table 2. Individual Pharmacokinetic, Pharmacogenetic data and Maternal/Neonatal Outcomes for Women

PROM=Premature Rupture of Membranes; GDM=Gestational Diabetes Mellitus; PPH=PostPartum Haemorrhage; GH= gestational Hypertension; RDS=Respiratory Distress Syndrome; SGA=Small for Gestational Age; APGAR=Appearance, Pulse, Grimace, Activity, Respiration; EM= Extensive Metabolizer; IM=Intermediate Metabolizer; PM= Poor Metabolizer; RP= Rapid Metabolizer; UM= Ultrarapid Metabolizer; PL= Plasma Level; N.A.=not available

Figure 1. Plasma Level vs Daily Dose of Sertraline, Escitalopram, Venlafaxine ER, Paroxetine (** Poor Metabolizers; *Intermediate Metabolizers)