Postpartum Bleeding in Pregnant Women Receiving SSRIs/SNRIs: New Insights From a Descriptive Observational Study and an Analysis of Data from the FAERS Database

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ABSTRACT

Purpose: To date, the available data on the relationship between the use of selective serotonin reuptake inhibitors (SSRIs) or the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine and postpartum hemorrhage (PPH) are conflicting and have not been extensively investigated, especially in terms of plasma drug concentrations. We performed data mining of antidepressant-induced PPH reported to the US Food and Drug Administration's Adverse Event Reporting System database, to assess the strength of the potential association between antidepressant pharmacotherapy and PPH in pregnant women. Concurrently, we carried out a descriptive observational population (pregnant women) analysis of the correlation between the plasma concentrations of SSRIs/SNRIs used during pregnancy and the extent of bleeding at delivery.

Methods: A disproportionality analysis of individual case study reports of PPH associated with SSRIs or venlafaxine in pregnant women was performed. Reporting odds ratio was used as a measure of disproportionality analysis. Pregnant women treated with an SSRI or SNRI (venlafaxine) for depressive or anxiety disorder and who consented to plasma drug concentration monitoring at the time of delivery were recruited. Plasma drug concentration assay was performed according to validated LC-MS/MS. Based on plasma drug concentrations, patients were classified into 1 of 2 groups, in therapeutic range or below therapeutic range for the drug administered, in accordance with the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie guideline, and correlations with blood loss were identified, with *PPH* defined as a blood loss of >500 mL.

Findings: Only 43 Individual Case Safety Reports (ICSRs) reported at least one SSRIs or venlafaxine as suspect drug in 14 years (database analyses). Forty-three women were enrolled in the study population (observational study). In 24 patients (55.8%) the plasma drug concentration was below the therapeutic threshold. Unexpectedly, the mean blood loss in the below-range group was significantly higher than that in the in-range group. PPH occurred in 30% of women: in 9.3% and in 20.7% of patients in the in-range and below-range groups, respectively.

Implications: Although preliminary, these data indicate a rather good tolerability profile of SSRIs/SNRIs regarding postpartum bleeding. Moreover, they suggest that keeping the plasma levels of SSRIs/SNRIs low as a precautionary measure does not

Accepted for publication June 23, 2019
https://doi.org/10.1016/j.clinthera.2019.06.008
0149-2918/$ - see front matter

reduce postpartum bleeding, which was higher in the below-range group. The findings from this study suggest that the use of therapeutic drug monitoring in pregnancy, a period in which multiple variables affect drug metabolism, may allow for better treatment customization, with subsequent advantages in terms of tolerability and efficacy of treatment. (*Clin Ther.* 2019;41:1755–1766) © 2019 Published by Elsevier Inc.

Keywords: antidepressants, FAERS database, postpartum bleeding.

INTRODUCTION

The prevalence of depressive disorders is 18.4% among pregnant women[1] and 19.2% among mothers in the first 6 months after delivery. The estimated prevalences of depression requiring treatment are 12.7% in pregnant women and 7.1% in the first 6 months after delivery. Anxiety disorders have a prevalence that varies between 4% and 39%, depending on the study, with comorbidity of depression and anxiety of up to 50%.[2,3]

Several studies have shown that depression not treated during pregnancy may have negative consequences on childbirth, on the postpartum period, and on the development of both the fetus and the newborn[4]; these consequences may include severe relapse,[5] preterm birth and low birthweight,[6] preeclampsia,[7] hypertension,[8] and an increased risk for psychiatric disorders in the child and problems with attachment.[9,10]

Selective serotonin reuptake inhibitors (SSRIs) are recommended by psychiatrists as the first-line treatment of depression in the peripartum period, with increased use in recent years. From recent studies, between 2% and 9% of women in Western countries indicated that they would take an SSRI in pregnancy if one were recommended.[11]

The prevalences of postpartum hemorrhage (PPH) during vaginal delivery and cesarean section are 4% and 6%, respectively. PPH may lead to organ failure, shock, compartment syndrome, thrombosis, sepsis, acute respiratory distress syndrome, anemia, and the need for intensive care hospitalization and/or transfusion,[12,13] and PPH is the cause of about one fourth of deaths related to childbirth.[14]

A possible correlation between the use of a selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor (SSRI/SNRI) and an increased risk for bleeding has been suggested based on an increase in gastrointestinal bleeding.[15] However, the relationship between the use of an SSRI or SNRI in pregnancy and PPH is still controversial and not well characterized.[16]

Therapeutic drug monitoring (TDM) is commonly recommended for optimizing the dosage of drugs. In pregnant women, in whom physiologic changes may lead to altered pharmacokinetics, Matsui[17] has recommended TDM for guiding therapy.

TDM of SSRIs, however, has not yet been implemented in routine clinical practice because SSRIs are considered well-tolerated medications with wide therapeutic ranges. In agreement with the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) guideline,[18] however, significant associations between the plasma concentrations of SSRIs and clinical outcomes have emerged in terms of both efficacy and tolerability. Monitoring the plasma concentrations of these medications can therefore be particularly useful in pregnancy in order to address therapeutic choices and to facilitate better control of pathophysiology and the occurrence of potential complications.

In January 2019 we performed a disproportionality analysis of antidepressant-induced PPH reported to a large pharmacovigilance database, the US Food and Drug Administration (FDA)'s Adverse Event Reporting System (FAERS), to assess preliminarily the strength of the potential association between antidepressant pharmacotherapy and PPH.[19] Concurrently we carried out a retrospective TDM-based study in order to assess the possible association between the extent of bleeding and the plasma concentration of SSRI/SNRI at delivery, in women with anxiety disorder or depression treated with these medications during pregnancy.

PATIENTS AND METHODS

Data Source

The FAERS is a database available for public access; it contains information related to postmarketing individual case safety reports (ICSRs) of adverse events (AEs) submitted by health care professionals and patients/consumers on a voluntary basis. The database is updated quarterly and designed in

accordance with the international tolerability reporting guidance issued by the International Conference on Harmonisation (ICH). AEs reported to the FAERS are coded using the Medical Dictionary for Regulatory Affairs (MedDRA) preferred terms. In the present study, we used OpenFDA, an innovative platform providing access to FDA data, which is an Elasticsearch (https://www.elastic.co/solutions/app-search)–based application programming interface (API) that provides publicly available FDA data on drugs, medical devices, and foods.

Data Acquisition

The OpenFDA API returns individual results as JavaScript Object Notation (JSON) by default; it returns the latest version of every report with the same identification number. All of the zipped JSON end points for drug events from the first quarter of 2004 (representing the beginning of FAERS data with free availability) through to the first quarter of 2018 were downloaded from the OpenFDA download webpage (https://github.com/FDA/openfda; last accessed July 28, 2018). A local server containing all downloaded JSON end points for OpenFDA API was set up as described on OpenFDA GitHub (https://open.fda.gov/tools/downloads). To search for AEs, we searched by fields specific to the drug/event.json end point and constructed our queries as guided by OpenFDA. Specific queries were constructed to identify all Cases of interest.

Selection of Cases and Noncases

Cases were defined as all ICSRs where at least 1 drug from the World Health Organization–defined Anatomical Therapeutic Chemical Classification (https://www.whocc.no/atc_ddd_index) N06AB (SSRIs) or N06AX16 (the SNRI venlafaxine) recorded as possibly related to AEs, along with at least 1 MedDRA lowest-level term, *postpartum hemorrhage*, *third stage postpartum hemorrhage,* or *bleeding postpartum*. In OpenFDA data, not all variables are indexed or have harmonized fields; therefore, we further queried data for different searchable fields with all possible variants of proprietary/nonproprietary names of drugs of interest. *Noncases* (controls) were defined as all other adverse drug reactions (ADRs) reported in the database during the same period of time (ie, all ADR reports without the outcome of interest). Figure 1 shows the selection of PPH associated with the drugs of interest (SSRIs or venlafaxine).

Data Processing

The individual results returned by the API as JSON were parsed into .CSV format by JavaScript library (https://github.com/FDA/openfda). The ICH string field values for age, age group, sex, and patient drug characterization were converted into their reference values as defined in ICH E2b/M2 Standards version 2.1 (http://estri.ich.org/e2br22/ICH_ICSR_Specification_V2-3.pdf). Because FAERS may sporadically contain duplicate reports, in Cases of reports submitted by both the consumer and the sponsor or intentional multiple reporting, data were further scrutinized manually based on similarities in patients, ADRs, and medicinal product data. Duplicate records were detected and deleted accordingly. Drug name text-mapping was accomplished by normalization of multiple drug names into a single generic name by automated matching processes through a SQL-database schema. Later, an open-source program, OpenRefine (http://openrefine.org; a tool for cleaning and transforming disordered data) was used to standardize drug name variants in the dataset to make them consistent with the international Anatomical Therapeutic Chemical Classification nonproprietary nomenclature.

Data Analysis

We used disproportionality analysis as a validated method of tolerability signal detection, to compare the likelihood of risk (PPH) among pregnant women exposed to an SSRI/SNRI. Reporting odds ratios (RORs) were used as a measure of disproportionality analysis. This method allows for the comparison of drug exposure among Cases and noncases by calculation of the ROR and their corresponding 95% CIs. This is a validated method of tolerability signal detection.[50] For each drug, the ROR was calculated as (a/c)/(b/d), where *a* is the number of PPH reports considered as possibly related to a drug of interest, *b* is the total ADRs except PPH events considered as possibly related to a drug of interest, *c* is the number of PPH reports considered as possibly related to any drug other than the drugs of interest, and *d* is the total ADRs, except PPH events, considered as possibly related to any drug other than the drugs of interest.

The number of Cases with an outcome of interest was compared with the number of cases reported in

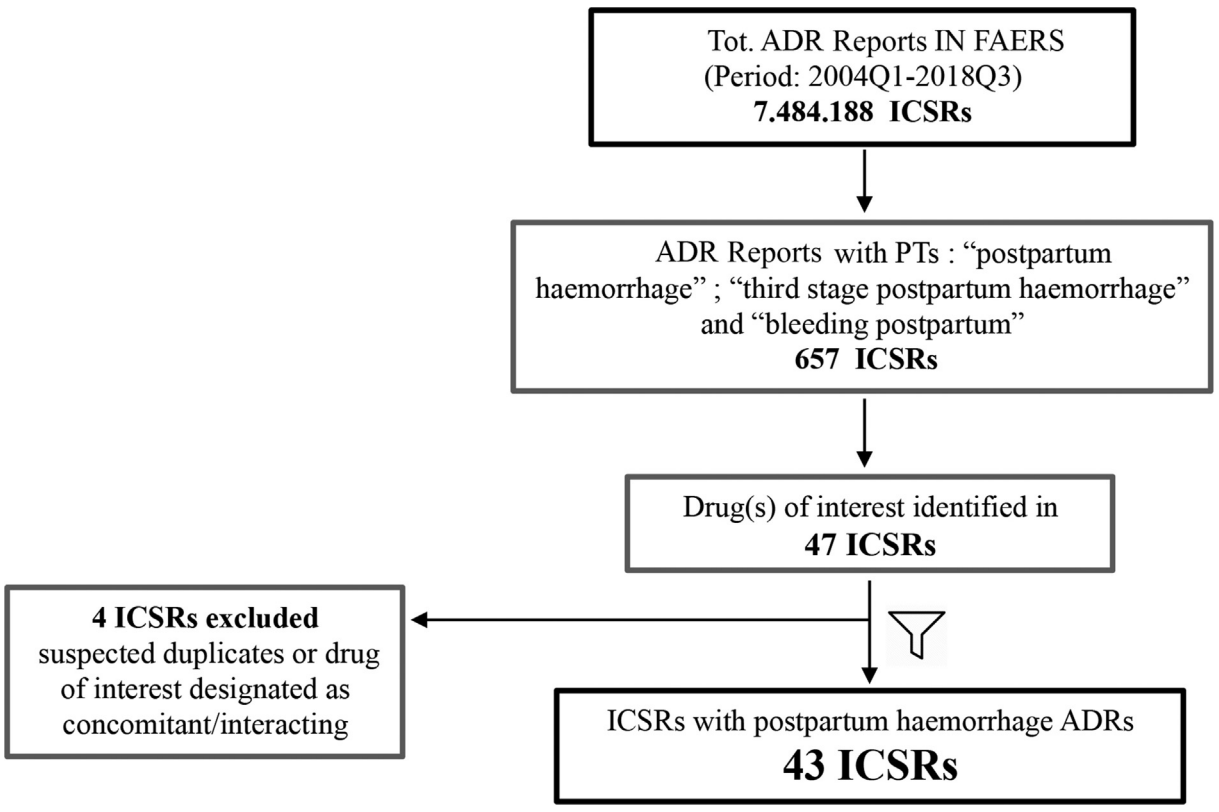

Figure 1. Selection of Cases of maternal/fetal hemorrhagic adverse events associated with drug of interest (selective serotonin reuptake inhibitors or venlafaxine). ADRs = adverse drug reactions; ICSRs = individual case safety reports; PT = MedDRA preferred term; Q = quarter.

each group of preferred terms for drugs other than the drugs of interest. Disproportionality analysis was based on unique drug–event combinations with at least 5 occurrences. A *signal of disproportionate reporting* was considered when the lower limit of the 95% confidence interval (CI) of the ROR is greater than one. Cases and controls with no information on age or sex were excluded, as the final step in the preparation of the dataset.

Study Population: Subjects and Outcome Assessment

This observational study was carried out between 2011 and 2017 to assess in a descriptive way the relationship, if any, between postpartum bleeding and consumption of an SSRI/SNRI during pregnancy. Pregnant women were recruited from the Psychopharmacological and Pregnant Outpatients Department at Depressive Treatment Center (Milan, Italy); or from the Antenatal Clinic, ASST Fatebenefratelli-Sacco University Hospital (Milan, Italy).

Inclusion criteria were as follows: a diagnosis of depressive disorder and/or anxiety disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th *Edition* (DSM-5) criteria; ongoing psychopharmacologic treatment with an SSRI or SNRI; singleton pregnancy; and age ≥18 years.

Exclusion criteria were as follows: the presence of a psychiatric disorder other than depressive disorder and/or anxiety disorder; and concurrent treatment with a psychopharmacologic medication with the exception of benzodiazepines, up to a dose equivalent to 0.5 mg of alprazolam.

The outcome of *PPH* was defined as a blood loss of >500 mL[20] as reported in the medical records of patients.

All patients provided written informed consent before any study procedure. The study was approved by the local ethics committee (Luigi Sacco University Hospital, Milan, Italy).

Plasma Drug Concentration Analyses at the Time of Delivery

Blood samples for the measurement of plasma drug concentrations were collected at delivery and then handled on ice. Plasma was separated by centrifugation and stored at −20°C until analysis. Plasma concentrations of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine were quantified using an LC-MS/MS method developed and validated in the centralized pharmacokinetics laboratory of the pharmacology unit.[21] With this LC-MS/MS method, the lower limit of quantification of all analytes was 5 ng/mL. The performance of the method 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). In accordance with the AGNP guideline,[22] we considered the following ranges of drug concentrations as therapeutic: citalopram, 50 to 110 ng/mL; escitalopram, 15 to 80 ng/mL; fluoxetine (plus the active metabolite), 120 to 500 ng/mL; paroxetine, 20 to 65 ng/mL; sertraline, 10 to 150 ng/mL; and venlafaxine (plus the active metabolite), 100 to 400 ng/mL.

Statistical Analysis

All of the variables studied were subjected to statistical analysis. For quantitative variables, ANOVA was carried out using the F test and the Shapiro-Wilk normality test, followed by the Mann-Whitney U test. Contingency analysis between the 2 groups was carried out using the Fisher exact test. The significance level was considered as $P < 0.05$. For statistical processing, we used the Prism 5 software package (GraphPad Software, San Diego, CA).

RESULTS

Postpartum Hemorrhage Reported to the FAERS Database

In the FAERS database, 657 Cases were related to PPH, of which 43 ICSRs reported at least one SSRIs or venlafaxine as suspect drug. The mean (SD) age of the patients was 31.5 (5.92) years (range, 17−42 years). Detailed counts of cases for antidepressant drugs with co-reported AEs are presented in Table I. Among the antidepressant drugs included in the study, sertraline (12 cases), venlafaxine (10 cases), and escitalopram (8 cases) were most frequently reported in association with PPH AEs. Overall, the preferred terms *drug exposure during pregnancy* and *exposure during pregnancy* were the most frequently co-reported AE terms.

The overall ROR of all antidepressant drugs included in our analysis was 3.56 (95% CI, 2.61−4.85), the highest values were observed with fluoxetine (ROR = 6.42; 95% CI, 3.05−13.53), escitalopram (ROR = 4.38; 95% CI, 2.18−8.80), and sertraline (ROR = 3.25, 95% CI. 1.84−5.76) (Table II). Moreover, we performed data mining of the FAERS in order to identify similar Cases of postpartum bleeding related to the use of bupropion a nonserotonergic antidepressant. However, no cases were detected in the same period of observation (2004-2018).

Study Population Characteristics

The study population included 43 pregnant women (age range, 18-45 years) treated with an SSRI/SNRI for the duration of pregnancy for the psychiatric diseases summarized in Table III. All of the patients were affected by an anxiety or depression disorder for which continuing the therapy during pregnancy was considered necessary by the personal psychiatrist. The drugs administered were the following: sertraline, in 20 patients (46.6%); paroxetine, in 11 patients (25.6%); escitalopram, in 6 patients (13.9%); fluoxetine, in 2 patients (4.7%); citalopram, in 1 patient (2.3%); and venlafaxine, in 3 patients (6.9%).

Plasma Drug Concentration of SSRI/SNRI and Postpartum Hemorrhage

Analysis of plasma drug concentrations was carried out on samples collected at delivery. The plasma drug concentrations of each drug are shown in Table IV. Therapeutic plasma drug concentration was reached in 19 patients (44.2%), according to the AGNP guideline. In 24 patients (55.8%), the drug concentration measured was below the therapeutic threshold. Considering the type of SSRI/SNRI administered, 55.0% of patients taking sertraline reached the therapeutic drug concentration, while this

Table I. Individual case safety reports of postpartum hemorrhage (PPH) with antidepressant drugs, with the 10 most frequently reported adverse drug reactions (ADRs), by MedDRA co-reported preferred term.

Antidepressant Drug	Serious PPH/Total PPH Cases	Co-reported ADRs
Sertraline	12/12	Maternal exposure during pregnancy (7), exposure during pregnancy (4), fetal death (4), and premature delivery (2), forceps delivery (2), preeclampsia (2), induced labor (2), prescribed overdose (2), transfusion (2), polyhydramnios (2)
Escitalopram	8/8	Maternal exposure during pregnancy (4), pregnancy (3), placental disorder (2), fetal death (2), forceps delivery (2), polyhydramnios (2), induced labor (2), premature delivery (2), paresthesia (1), depression (1)
Citalopram	7/7	Exposure during pregnancy (4), maternal exposure during pregnancy (3), perinatal depression (2), candida infection (1), breast hemorrhage (1), calculus urinary (1), crying (1), pain (1), paresthesia (1), pregnancy (1)
Fluoxetine	7/7	Exposure during pregnancy (3), cesarean section (2), anemia (2), maternal exposure during pregnancy (2), pulmonary edema (1), cardiac failure (1), urinary tract infection (1), cephalopelvic disproportion (1), premature labor (1), depression (1)
Paroxetine	2/2	Anemia (1), gestational hypertension (1), hemoglobin decreased (1), maternal exposure during pregnancy (2), postpartum uterine subinvolution (1), pregnancy (1), retained placenta or membranes (1), uterine contractions abnormal (1)
Venlafaxine	10/10	Maternal exposure during pregnancy (4), pregnancy (1), pyelonephritis (1), gestational diabetes (1), cesarean section (1), gestational hypertension (1), prolonged labor (1), induced labor (1), retroplacental hematoma (1)

event occurred only in 35.0% of patients taking citalopram, escitalopram, fluoxetine, paroxetine, or venlafaxine.

According to the plasma concentrations of the drugs, patients were then divided in 2 groups; those with a plasma drug concentration above (in-range) and those with a plasma drug concentration below the minimum effective dose (below-range) and were analysed for postpartum bleeding. Unexpectedly, the mean blood loss in the below-range group was significantly higher than the mean of the blood losses in the in-range group (Figure 2). PPH (blood loss of >500 mL) occurred in 30% of women: in 9.3% and in 20.7% of patients in the in-range and below-range groups, respectively (odd ratio = 0.4444; 95% CI, 0.1120−1.764).

In order to exclude the type of delivery as a potential confounding factor of the analysis, we took into consideration in the 2 patient groups the distribution of vaginal and cesarean sections.

The Fisher exact test excluded a preferential distribution of cesarean sections in the group of patients with plasma concentrations below therapeutic range, suggesting that the increase in bleeding in this group was not dependent on the type of delivery (odd ratio = 0.900; 95% CI, 0.2697−3.003). The difference in blood loss between the in-range and below-range groups was significant in the case of vaginal delivery ($P = 0.0267$), while no difference was observed in the case of cesarean section ($P = 0.1687$) (Figure 3).

DISCUSSION

In the past few decades, the prevalence of PPH in pregnant women has increased significantly.[23,24] To date, the causes of this increase are not clear, as significant changes in the known risk factors (multiparity, operative vaginal delivery, previous PPH, placental alterations, use of oxytocin, maternal body mass index, distended uterus) have not

Table II. Reporting odds ratios for the association between different antidepressants and postpartum bleeding.

Drug	No. of Cases	ROR (95% CI)
Any drug of interest	43*	3.56 (2.61−4.85)
Sertraline	12	3.25 (1.84−5.76)
Escitalopram	8	4.38 (2.18−8.80)
Citalopram	7	2.77 (1.32−5.83)
Fluoxetine	7	6.42 (3.05−13.53)
Paroxetine	2	Not applicable
Venlafaxine	10	2.92 (1.56−5.45)

ROR = reporting odds ratio.
*Some reports contained >1 suspected antidepressant drugs. For this reason, the total number of reports in which an individual antidepressant (n = 46) was mentioned as the suspected drug was higher than the total number of reports in which an antidepressant drug was mentioned as the suspected drug (n = 43).

occurred; a possible role of as-yet non-investigated risk factors has thus to be studied.[24–29]

Among such possible risk factors is the use of drugs. The use of SSRIs/SNRIs has increased over the years; these drugs have been reported to be potentially associated with an increased risk for bleeding in some studies, whereas in others the association is unclear.

A systematic review by Bruning et al[16] analyzed data from 4 observational studies.[20,30–32] Among these, 2 cohort studies[15,30] showed an increase in PPH associated with the use of SSRIs or SNRIs, while the other 2 studies (1 retrospective[31] and 1 case control[32]) showed no association. A recent review[33] analyzed data from 8 studies pinpointing a higher risk associated with the use of SSRIs, and, even more so, of SNRIs in the last month of pregnancy.[15,20,30,32,34–37] The subanalyses carried out to limit confounding factors confirmed the data; in addition, a greater risk for bleeding even with antidepressants of classes other than SSRI/SNRI (nefazodone, trazodone, mirtazapine) was highlighted. The findings from a population-based cohort study carried out in Canada suggested that exposure to SNRIs in late pregnancy significantly increases the risk for PPH, whereas similar exposure to SSRIs did not significantly increase the risk.[35] More recently, an article by Heller et al[38] showed an increase in PPH linked to treatment with not only SSRIs but also other psychopharmacologic therapies (antipsychotics, mood stabilizers, and benzodiazepines).

Data-mining methods applied to databases of spontaneous reporting systems are frequently used in quantitative signal detection and are of high importance in the tolerability assessment of drugs in the postmarketing setting, above all in complicated clinical settings.[19,39,40]

Ours is the first disproportionality analysis aimed at evaluating the strength of the potential association between antidepressant pharmacotherapy and PPH, by using a large-scale pharmacovigilance database, FAERS.

In accordance with findings from previous studies,[30,38] we found that treatment with either an SSRI or venlafaxine was statistically associated with PPH (the highest ROR was detected with fluoxetine: 6.42; 95% CI, 3.05−13.53), supporting the need for further investigation.

Depression is common during pregnancy, and the use of antidepressants during gestation has increased over the past 20 years[41,42]; SSRIs are the most frequently prescribed antidepressants in pregnant women, with a reported prescribing rate of >2% among pregnant women in the United States.[43,44] Despite the fact that there was an increased risk with all of the drugs included in the study (ROR = 3.56; 95% CI, 2.61%−4.85%), the reported number of PPH Cases (43) related to antidepressants identified in FAERS in a long period of observation (2004−2018) was very low considering all of the pregnant women exposed to SSRIs and suggests a rather good tolerability profile for these drugs in pregnancy in terms of PPH. The fact that no cases of PPH were detected with bupropion suggests a lower risk for bupropion-induced bleeding with respect to SSRIs.

Considering this evidence, it is on one hand surprising that so few Cases have been reported to the FAERS database; on the other hand, under-reporting might have led to an underestimation of the data.

It is worth mentioning that all of the analyses carried out had several limitations, including a non-unique definition of *PPH* (which varied between studies from >500 mL up to >1000 mL), the lack of sufficient data on the clinical and therapeutic implications of this complication, the presence of confounding factors (lifestyle habits, type of delivery) and the lack, in some Cases, of precise dose indications and gestational age at exposure to medications.

Table III. Characteristics of the study population.

Characteristic	Value
Age, mean (SD), y	34.6 (4.35)
Smoking history	7 (16.27%)
Alcohol use	1 (2.32%)
Pregnancy	
Spontaneous	40 (93%)
Assisted reproductive technology	3 (7%)
Comorbidity	
Hypothyroidism treated with levothyroxine	4 (9.3%)
β-Thalassemia, thalassemia minor	2 (4.65%)
Hypertension	2 (4.65%)
Polycystic ovary, endometriosis	2 (4.65%)
Cholestasis of pregnancy	1 (2.32%)
Ulcerative colitis	1 (2.32%)
Discoid lupus	1 (2.32%)
Epilepsy	1 (2.32%)
First trimester varicella infection	1 (2.32%)
Gestational diabetes	1 (2.32%)
Multiple sclerosis	1 (2.32%)
Other nonpsychopharmacologic therapy	
Levothyroxine	4 (8.57%)
Phenobarbital	1 (2.32%)
Nadroparin	1 (2.32%)
Ranitidine for hyperemesis gravidarum	1 (2.32%)
Methyldopa	1 (2.32%)
Nifedipine	1 (2.32%)
Ursodeoxycholic acid	1 (2.32%)
Delivery type	
Vaginal	22 (51.16%)
Cesarean section	21 (48.84%)
Diagnosis	
PD, GAD, other unspecified anxiety disorder, PTSD	17 (39.53%)
MDD	14 (32.56%)
MDD and personality disorder	5 (11.63%)
OCD	4 (9.30%)
PD, MDD	1 (2.32%)
MDD, OCD	1 (2.32%)
(Other unspecified) bipolar disorder, personality disorder	1 (2.32%)
BZD use	14 (32.56%)

BZD = benzodiazepine; GAD = generalized anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PD = panic disorder; PTSD = post-traumatic stress disorder.

Another fundamental limitation of all of these studies was that the plasma concentration of the medications was not considered in any of them. Pharmacokinetic properties are likely altered during pregnancy as a result of physiologic and anatomic changes, including reduced gastric emptying and small-intestinal motility, altered body composition and organ blood flow, higher glomerular filtration rate, and the increased activity of some drug-metabolizing enzymes, such as cytochrome P450 2D6, that is involved in treatment with many antidepressants.[45] Currently, however, dosing regimens are often simply extrapolated from nonpregnant to pregnant women, entailing considerable risks for subtherapeutic or toxic drug effects in the mother and/or fetus.

In this study, we describe, for the first time, the entity of postpartum bleeding in relation to the plasma concentration of antidepressant drugs at the time of delivery. As expected we found a great interindividual variation in plasma concentrations, and more than the half of patients showed drug levels below the therapeutic range. In these women, the mean blood loss was higher than in the women with drug concentrations in the therapeutic range, irrespective of the type of delivery.

The use of pharmaceutical agents in pregnancy has increased in high-income countries in recent decades. Some of them, such as aspirin and other antiplatelet drugs, NSAIDs, and antihistamines are associated with bleeding.[46] A recent article showed that the risk for PPH was increased with concurrent exposure to antidepressants, aspirin, and β-agonists, but these effects were not statistically significant. None of the patients included in our study were taking these medications during pregnancy.[36]

Table IV. Plasma drug concentrations at the time of delivery.

Drug	No. of Patients	Dosage, mg/d	Plasma Drug Concentration, mean (SD), ng/mL	No. of Patients Below Range
Sertraline	20	25–125	18.185 (19.496)	9
Paroxetine	11	10–20	11.809 (13.479)	9
Escitalopram	6	5–10	17.033 (13.667)	4
Fluoxetine	2	20	181.900 (49.356)	0
Citalopram	1	20	<5.000	1
Venlafaxine extended release (ER)	3	75–150	151.900 (65.736)	1

Whereas the observed lower blood loss in pregnant women taking SSRIs with plasma concentrations above the minimum effective concentration may be coincidental, it may be worth considering the elevation of serotonin plasma levels associated with these drugs, and its effect on the myometrium.[47] Indeed, in the atonic postpartum uterus, the activation of serotonin receptors (ie, 5-HT2A and 5-HT_3) may protect against PPH by potentiating uterine smooth muscle contraction.[47–49]

The main limitation of the current observational descriptive study was the size of the sample, which might have decreased the statistical power of the results and which cannot allow for the assessment of an association, if any, between PPH risk and SSRI/SNRI TDM. On the same note, the low number of patients did not allow us to perform an analysis of the effects of SSRIs and SNRIs separately, and these data

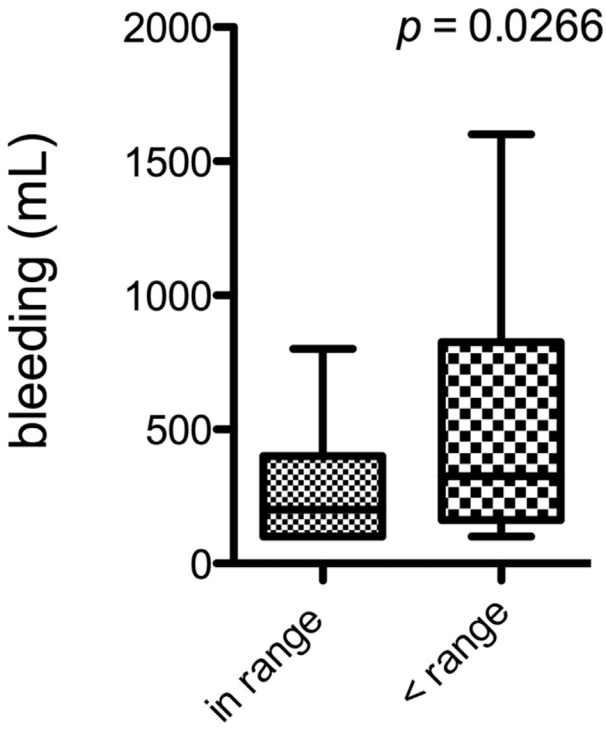

Figure 2. Median (IQR, minimum, maximum) postpartum bleeding in the in-range (n = 19) and below-range (< range) groups (n = 24). Statistical analysis was carried out using the Mann-Whitney *U* test. The significance level was considered as $P < 0.05$.

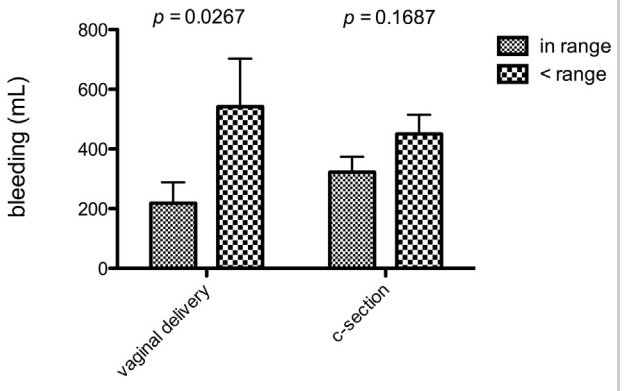

Figure 3. Mean (SD) postpartum bleeding in vaginal versus cesarean (c)-section delivery. Postpartum bleeding was evaluated in vaginal and cesarean section deliveries in the in-range and below-range (< range) groups. Statistical analysis was carried out using the Mann-Whitney *U* test. The significance level was considered as $P < 0.05$.

had thus to be considered together. Moreover, we could not assess systematically the compliance with drug treatment or when patients took the last dose of medication. Finally, it was not possible to eliminate all of the confounding factors (eg, smoking or alcohol use). The sample, however, was homogeneous with regard to personal data, diagnoses, and severity of psychopathologic conditions.

CONCLUSIONS

Because of the observational nature of the present study and the number of Cases investigated, this study has to be considered descriptive of a condition that needs to be examined through more extensive clinical trials. Our naturalistic setting represented the heterogeneity typical of a clinical-practice scenario, in which a high percentage of pregnant women treated with SSRIs/SNRIs at marketed doses showed subtherapeutic plasma concentrations of the drugs at delivery, and that this event was correlated with a significant increase in postpartum bleeding. While a potential protective effect of SSRIs/SNRIs on PPH cannot be established by our study, this study nonetheless corroborates their use during pregnancy. Moreover, this study highlights the importance of TDM in avoiding underdosing and subtherapeutic drug concentrations in special populations such as pregnant women.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

ACKNOWLEDGMENTS

C. Perrotta provided data interpretation, conceptualized and wrote the manuscript, and created the figures. F. Giordano collected and organized the data, contributed to data analysis, and contributed to the literature search. A. Colombo contributed to the study design, supervised the study, and reviewed the manuscript. C. Carnovale collected and analyzed the FAERS database data and reviewed the manuscript. M. Castiglioni, I. Di Bernardo, and F. Giorgetti collected and organized the data. P. Pileri contributed to the study design and supervised the collection of blood samples. E. Clementi supervised the drafting of the manuscript and critically reviewed the manuscript. C. Viganò, as the principal investigator of this study, was involved in the study design, supervised the study, interpreted the data, and conceptualized and reviewed the drafts of the manuscript. All of the authors were involved in the decision to submit the manuscript for publication; accordingly, they read and approved the final version of the manuscript. The authors like to thank Dr. Faizan Mazhar (enrolled in the Ph.D. in Experimental and Clinical Pharmacological Sciences, University of Milano that supports his fellowship) for assistance with statistical analysis in the context of FAERS data-mining and Dr. Sara Baldelli and Dr. Dario Cattaneo, ASST Fatebenefratelli Sacco, Milan, Italy, for their support.

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