



## CASE REPORT

# Intermenstrual Vaginal Bleeding Due to Sertraline Treatment: A Case Report

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### ABSTRACT

Sertraline and other serotonin reuptake inhibitors are widely used in the treatment of psychiatric disorders such as anxiety disorders and depression. Hematological adverse effects related to sertraline are uncommon; most of the reported cases presented with vaginal bleeding, epistaxis, purpura, hematuria, and rectal bleeding. SSRIs may increase the risk of bleeding through different mechanisms. The most emphasized mechanism is lowering platelet aggregation by reducing serotonin reuptake in platelets. This report includes a case of intermenstrual vaginal bleeding due to the use of sertraline and a review of the relevant literature. We aimed to draw clinician's attention to this side effect of SSRIs.

**Keywords:** Adverse effect, sertraline, vaginal bleeding

## INTRODUCTION

Sertraline is a selective serotonin reuptake inhibitor (SSRI) antidepressant that inhibits serotonin reuptake in the central nervous system, thrombocytes, and gastrointestinal system. Selective serotonin reuptake inhibitors are widely used in the treatment of psychiatric disorders (1). Most common side effects of SSRIs are dizziness, tremor, diarrhea, fatigue, ejaculation disorder, and insomnia (2). The increased risk of bleeding is a rare side effect of SSRIs. Because of the widespread use of these drugs, this side effect is clinically significant. Many mechanisms have been studied for the increased risk of bleeding with SSRIs.

Hematological side effects of SSRIs are related to their impact on peripheral serotonin. More than 99% of the serotonin in the body is stored within platelets. Peripheral

serotonin plays a vital role in platelet aggregation and regulation of vascular tonus (3,4). SSRIs elevate central nervous system serotonin while reducing the serotonin within the platelets. Hemostasis includes various components; vasoconstriction and platelet aggregation (primary hemostasis), clotting, antithrombotic activity and fibrinolysis (5). Serotonin released from platelets is known to have a role in intervention of the hemostatic response to vascular damage and inducing vascular constriction and platelet aggregation. The SSRIs inhibit the reuptake of serotonin into platelets, reducing platelet serotonin stores, and lowering platelet aggregation (6). Also, long-term treatment with SSRIs upregulates the expression of glycogen synthase kinase 3 $\beta$  (GSK3B) on platelets; GSK3B acts as a negative regulator of platelet function and thrombosis and might contribute to bleeding risk with SSRI use (7). SSRIs increase gastric acidity, which is the most likely cause of upper gastrointestinal bleeding in the majority of SSRI-related bleeding cases (8). The combined use of SSRIs with NSAID (non-steroidal anti-inflammatory drugs) and warfarin increase the risk of bleeding (9,10).

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In this article, we aimed to present a case of intermenstrual vaginal bleeding associated with sertraline and to review the relevant literature.

## CASE PRESENTATION

A 34-year-old female patient admitted to the psychiatric outpatient clinic for complaints of growing discomfort, restlessness, palpitations, and feeling unable to breathe for last month. No pathology detected after blood workup and cardiology consultation, and sertraline 50 mg/day was started with a diagnosis of anxiety disorder. On the third day of the treatment, she consulted for sudden vaginal bleeding. Her last menstrual bleeding was 12 days ago. She had no history of menstrual irregularities, vaginal or another abnormal bleeding. Bleeding disorder, trauma, and self-injurious behavior were not mentioned in family history. She had no history of vitamin, herbal supplement and drug use other than sertraline for the last month. The hematology and gynecology departments consulted the patient. The blood test results were within the normal range, and a hematology specialist suggested that these complaints were not associated with any hematologic pathology. Blood tests results; white blood cell 8.200 (4600-10200) cells/mm<sup>3</sup>, red blood cells 4.4 (4.04-6.13) million cells/mm<sup>3</sup>, platelets 270.000 (142000-424000) /mm<sup>3</sup>, PT 13 (9.75-13.94) seconds, PA 100% (80-100), aPTT 30 (17.6-31.6) seconds, bleeding time 4 (2-7) minutes, clotting time 4 (2-10) minutes, fasting blood glucose 88 (70-100) mg/dL, urea 35 (17-43) mg/dl, creatinine 0.9 (0.51-0.95) mg/dl, AST 25 (0-40) u/l, ALT 25 (0-40) u/l, GGT 18 (2-40) u/l, TSH 3.2 (0.35-4.94) u/l, T4 5.5 u/l (5.4-11.5), free T3 3.5 u/l (2.62-5.69). No abnormality detected in abdominal and uterine ultrasonography. Endometrial biopsy and obstetric examination performed by an Obstetric Gynecology specialist and no pathology was detected. The Naranjo Adverse Drug Reactions Probability Scale has been performed, given a score of 6, which shows a probable relationship between sertraline treatment and vaginal bleeding (11). Following the cessation of sertraline treatment, the bleeding terminated within 24 hours. The

bleeding did not recur at weekly controls, and bupropion 150 mg/day, started for the patient's anxiety symptoms, and bleeding did not recur within one month follow up period.

## DISCUSSION

The most extensive data on hematological side effects of the selective serotonin reuptake inhibitors (SSRIs) in the literature are defined in Australian drug adverse effect reports (12). Most of the cases are superficial bleedings such as petechia, purpura, ecchymosis, and epistaxis (13-18). Besides gastrointestinal bleedings, SSRIs have been reported to increase the risk of intracranial bleeding, postoperative bleeding risk, and blood transfusion requirements (19-22). In some cases, side effects were dose-dependent (17,23). In literature, few cases of vaginal bleeding that are thought to be related to the use of antidepressants have been reported (24-28). A small number of large-scale research results, other than case presentations, have not provided definitive evidence that serotonin reuptake inhibitors increase menstrual bleeding (6). A large, multicenter, case-control study reported the incidence of antidepressant-related menstrual disorders at 14.5% (29). No menstrual side effects have been reported in a meta-analysis study about the efficacy of SSRIs in premenstrual syndrome (30). Another large cohort study found no association between any class of antidepressants and vaginal bleeding during pregnancy or postpartum hemorrhage after vaginal or caesarian delivery (31). Only one hospital-based cohort study reported an SSRI-increased postpartum vaginal bleeding risk after vaginal delivery, relative to women who did not use SSRIs. The amount of bleeding (484-384 ml) was also higher in SSRI users relative to nonusers (32).

Lack of any hematologic and obstetric pathology, trauma or drug use other than sertraline, and no abnormality in hematologic tests that would explain the bleeding, and improvement of bleeding after cessation of sertraline led us to believe that the bleeding might be related to sertraline. Nevertheless, there are some limitations of this report. We have not performed

hematological evaluations for inherited disorders like von Willebrand Disease. We would have more definitive evidence, if there had been a laboratory abnormality that turned back after withdrawal of the drug or if we had retry sertraline and she had developed bleeding again. Also, we would reduce the dose before stopping the drug. In this case, we discussed the possible process with the patient and decided to the cessation of treatment until bleeding improved.

Which agents could be chosen for the treatment of patients that developed bleeding due to SSRIs? This decision must be made on an individual basis. We chose bupropion in this case, an antidepressant that does not inhibit serotonin reuptake after the cessation of sertraline treatment and bleeding did not recur. A few studies support the use of another SSRI (16). A meta-analysis study of 3981 publications, showed no significant difference between bupropion, mirtazapine, and SSRIs for bleeding risk (33).

As a result; this case report and studies in the literature show that sertraline and other SSRIs increase the risk of bleeding. Patients are at risk of abnormal bleeding primarily during the period of actual use (6). The inhibition of platelet aggregation and vasoconstriction by inhibiting the reuptake of serotonin in platelets is the possible cause of this side effect. This effect may be dose-dependent. Clinicians should be cautious about the combined use of SSRIs and other drugs that affect platelet function and the risk of bleeding in patients with liver disease, low platelet count or platelet dysfunction. The abnormal vaginal bleeding is a rare, but serious side effect of SSRIs and should be taken consideration by clinicians.

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**Conflict of Interest:** No conflict of interest.

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