Original Article

DOI: 10.5582/ddt.2024.01071

A pharmacovigilance study based on the FAERS database focusing on anticoagulant and hormonal drugs that induce vaginal hemorrhage

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SUMMARY: Numerous medications have been associated with an increased risk of vaginal hemorrhage in women. In this study, we analyzed data from the FDA Adverse Event Reporting System (FAERS), focusing on reports of drug-induced vaginal bleeding in women. Risk signals were assessed using disproportionality analyses, specifically the reporting odds ratio (ROR) and the proportional reporting ratio (PRR), to identify significant associations between drugs and adverse events. We found that anticoagulants, hormonal drugs, psychotropic drugs, hypoglycemic agents, antineoplastic agents, anti-inflammatory drugs, immunological agents, and some drugs for osteoporosis were significantly associated with the risk of vaginal hemorrhage. Hormonal drugs, anticoagulants, and particularly antifungal agents were attributed to a notably high proportion of vaginal hemorrhage cases, necessitating further investigation into the underlying mechanisms. Therefore, precise clinical management of medications and optimization of treatment regimens are necessary to reduce the risk of vaginal hemorrhage and improve safety.

Keywords: Pharmacovigilance, drug-Induced vaginal hemorrhage, FDA Adverse Event Reporting System, drug safety

1. Introduction

Vaginal hemorrhage is a prevalent gynecological condition with various potential causes. Idiopathic vaginal hemorrhage in women of reproductive age is often associated with hormonal fluctuations (*1*), pregnancy-related conditions (*2*), endothelial changes (*3*), and structural abnormalities or genetic disorder (*4*) in the reproductive system.

Recent advancements in medical research and diagnostic technology have substantially improved the understanding of vaginal hemorrhage. Diagnostic imaging techniques such as hysteroscopy, ultrasonography (*5*), and magnetic resonance imaging (MRI) (*6*) help identify the cause of vaginal hemorrhage with increased accuracy. Additionally, a holistic patient evaluation, encompassing medical history, physical examinations, and laboratory investigations, is important for validating the cause of hemorrhage and designing targeted treatment strategies.

The clinical management of vaginal hemorrhage varies based on the etiology and the condition of patients. Treatment options may range from pharmacological interventions, which are particularly effective for hormonal imbalances, to surgical procedures necessary for addressing structural abnormalities, such as uterine fibroids or polyps (*7*). Furthermore, lifestyle modifications are a fundamental component of the clinical management of vaginal hemorrhage. The shift towards personalized medicine highlights the importance of customized treatment plans that enhance both therapeutic efficacy and patient satisfaction.

Hormonal drugs, especially those used in contraceptive or hormone replacement therapies, can induce vaginal hemorrhage in some women. Schrager *et al*. (*8*) reported that irregular vaginal hemorrhage was common in 70% of women after the use of long-acting progestin contraceptives such as depot medroxyprogesterone acetate injections and levonorgestrel subdermal implants. For many patients, this hemorrhage becomes more predictable and normalizes over time. Furthermore, anticoagulant drugs have been shown to increase the risk of vaginal hemorrhage. Jignesh *et al.* (*9*) reported that two-thirds of women aged 18-50 years on anticoagulant therapy experienced significant vaginal hemorrhage, which adversely affected their quality of life. These insights highlight the imperative for cautious medication use in women, emphasizing the importance of close monitoring of adverse effects to ensure the safest possible treatment regimens.

In this study, we investigated the drugs with a higher incidence risk of inducing vaginal bleeding by analyzing adverse event reports from the Food and Drug

Administration (FDA), providing crucial insights to improve drug safety in clinical practice.

2. Methods

2.1. Data source

The data used in this study were extracted from the FDA Adverse Event Reporting System (FAERS) database. This publicly accessible database compiles drug safety reports from patients, healthcare professionals, and pharmaceutical manufacturers. The dataset spans reports from the first quarter of 2004 to the first quarter of 2024.

2.2. Data selection

Initial data screening involved removing duplicate and incomplete entries from the dataset, resulting in 2,789 unique medications. Because the top 50 drugs filtered by the preferred terms (PTs) had a limited number of positive signals, which were insufficient for robust data analysis, the scope was expanded to the top 200 drugs for screening. To identify any potentially overlooked adverse events, further analysis and validation were conducted based on higher-level terms (HLTs) and higher-level group terms (HLGTs) in addition to the initial screening based on PTs. Eventually, 34 drugs with positive signals were identified and selected for analysis.

2.3. Ethical approval of studies

The FAERS database represents a global, spontaneous reporting system for drug-induced adverse events. The objective of this study was to conduct signal detection and analysis of drug safety using only publicly available, de-identified data. Therefore, ethical approval was not required. This study complies with the provisions of the Declaration of Helsinki.

2.4. Statistics analysis

Target drugs potentially inducing vaginal hemorrhage were identified by calculating positive signals using the reporting odds ratios (RORs) (*10*) and proportional reporting ratios (PRRs) (*11*). These measures are widely recognized in pharmacovigilance for evaluating the association strength between a drug and an adverse event. For the ROR, the criterion for detecting a positive signal was a lower limit of the 95% confidence interval (CI) exceeding 1, with at least three reported adverse events. For the PRR, a positive signal was indicated when the ratio exceeded 2 and the chi-square statistic (χ^2) was ≥ 4, with at least three reported adverse events (*12*). A drug meeting both criteria was considered to have a significant association with vaginal hemorrhage. The results were expressed as case counts (n) and percentages. Data analysis and visualization were performed using the R (version 4.2.3) software.

3. Results

3.1. Identification of all reports of suspected adverse drug events in FAERS

The data derived from the FAERS database spanning from the first quarter of 2004 to the first quarter of 2024 included 17,785,193 entries after deduplication. Of these entries, 38,608 entries were related to drug-induced vaginal hemorrhage, represented by 37,506 individual records. From an initial list of the top 200 drugs, 34 drugs were identified to have positive signals for inducing vaginal hemorrhage (Figure 1).

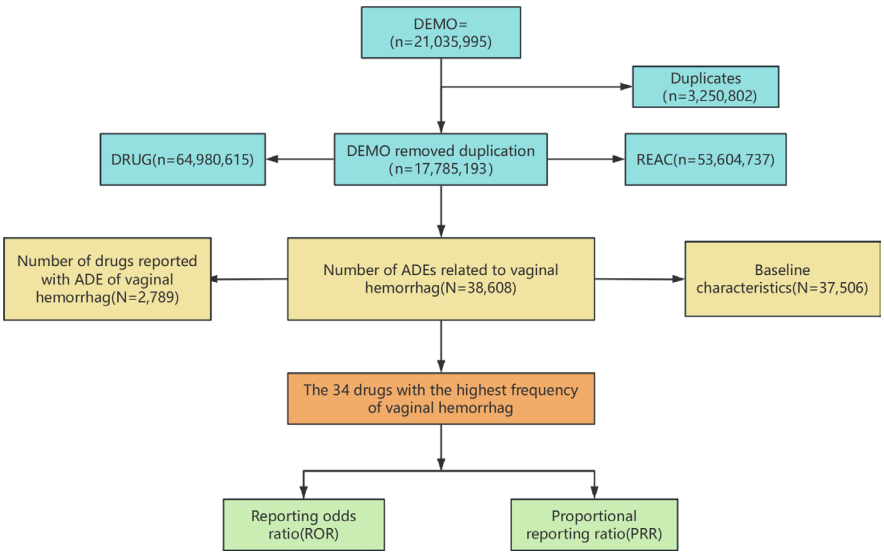

Figure 1. Flowchart demonstrating the protocol for the identification of reports of suspected adverse drug events (ADEs) in the FDA Adverse Event Reporting System (FAERS) database. The data were derived from the FAERS database spanning the first quarter of 2004 to the first quarter of 2024. Of the 200 drugs initially screened, 34 drugs were identified to exhibit positive signals for vaginal hemorrhage.

3.2. Reporters of drug-induced vaginal hemorrhage

Consumer reports comprised the majority of data on drug-induced vaginal hemorrhage, totaling 22,804 cases, followed by reports from physicians and other healthcare professionals, totaling 5,546 and 3,453 (10%) cases, respectively (Figure 2).

3.3. Number of ADEs reported per year

Since the inception of the FAERS database in 2004, the reporting of adverse drug events (ADEs) in the database has shown a year-over-year increase, with fewer reports being published initially owing to the nascent stage of the database and statistical methods. Notably, the number of reports began to increase in 2015, reaching a peak in 2016 with 3,847 cases, and continued to increase until a decline began in 2021 (Figure 3). This decline is most likely attributed to advancements in medical technology that reduced the occurrence of ADEs.

3.4. Positive drugs that induce vaginal hemorrhage

Initial analysis of the top 50 drugs based on the frequency of PTs revealed limited positive signals. Expanding the analysis to the top 200 drugs revealed 34 drugs with significant positive signals (Figure 4). Hormonal medications were prominently represented, with 14 drugs being identified. Levonorgestrel had the highest ROR at 201.97 (95% CI, 196.56-207.53), followed by medroxyprogesterone (ROR, 29.06; 95% CI, 10.79-78.23), mifepristone (ROR, 21.76; 95% CI, 18.65-25.38), estradiol patches (ROR, 14.02; 95% CI, 12.49-15.73), estradiol and norethindrone acetate (ROR, 20.47; 95% CI, 17.28-24.25), and leuprorelin acetate (ROR, 19.46; 95% CI, 18.19-20.8). Among the

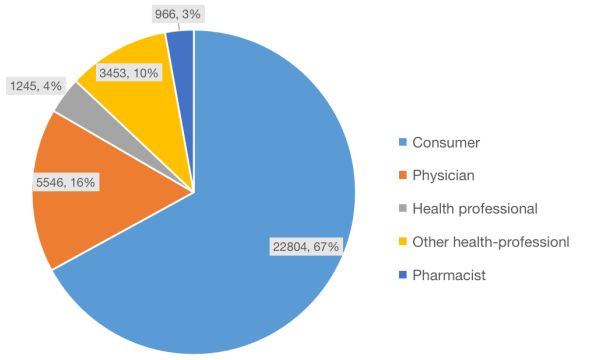

Figure 2. Reporters of ADEs related to vaginal hemorrhage. The majority of ADE reports were submitted by consumers, followed by physicians, pharmacists, and other healthcare professionals.

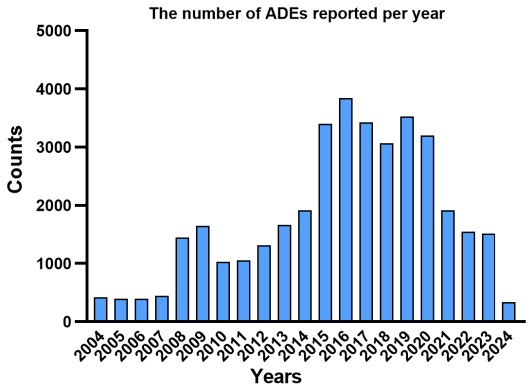

Figure 3. Number of ADEs reported per year. In the FAERS database, the number of ADE reports related to vaginal hemorrhage increased each year since database inception, peaking in 2016 and beginning to decline in 2021.

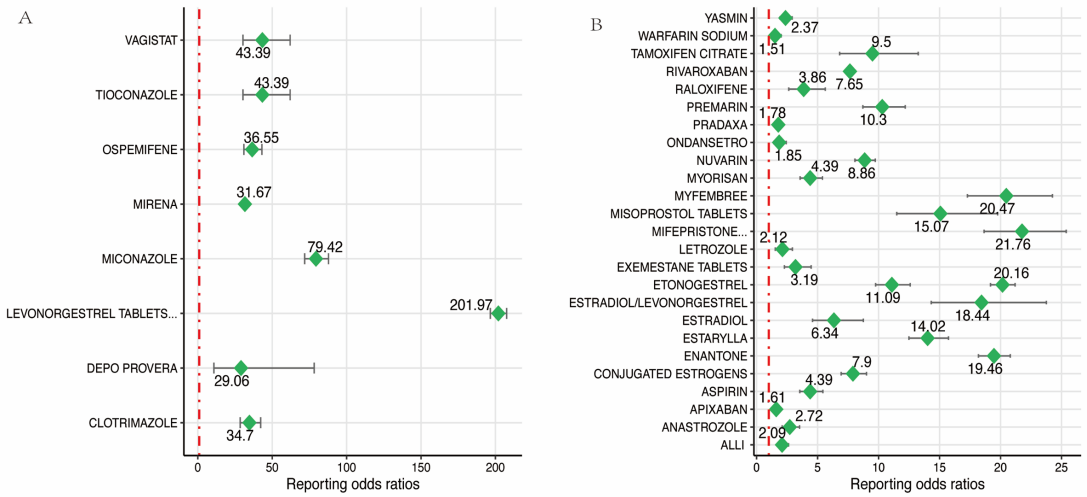

Figure 4. (A) RORs and 95% CIs of drugs with positive signals with ROR greater than 30. (B) RORs and 95% CIs of the remaining drugs with positive signals with ROR less than 30. Analysis of the top 200 drugs according to the PT revealed 34 drugs with positive signals. Among these drugs, hormonal and anticoagulant agents accounted for the largest proportions, followed by antifungal, psychotropic, anti-inflammatory, and hypoglycemic agents. Antifungal drugs had strong positive signals; however, their mechanisms of action in inducing vaginal hemorrhage warrant further investigation.

most common antifungal agents associated with vaginal hemorrhage, miconazole, clotrimazole, and terconazole had RORs of 79.42 (95% CI, 71.82-87.83), 34.71 (95% CI, 28.51-42.25), and 21.76 (95% CI, 18.65-25.38), respectively. Anticoagulants demonstrated positive signals, particularly in patients with cardiovascular and cerebrovascular diseases. These drugs included rivaroxaban (ROR, 7.65; 95% CI, 7.23-8.09), apixaban (a factor Xa inhibitor), aspirin (ROR, 4.39; 95% CI, 3.54-5.43), dabigatran etexilate, and warfarin. The anti-cancer drugs associated with vaginal hemorrhage included anastrozole (ROR, 2.72; 95% CI, 2.1-3.52), letrozole (ROR, 2.12; 95% CI, 1.53-2.94), exemestane tablets (ROR, 3.19; 95% CI, 2.28-4.47), and tamoxifen (ROR, 9.5; 95% CI, 6.81-13.25). In elderly individuals susceptible to osteoporosis, medications such as ospemifene (ROR, 36.55; 95% CI, 30.99-43.12) and raloxifene (ROR, 3.86; 95% CI, 2.64-5.63) were identified as having positive signals. Additionally, drugs with positive signals but lower frequencies included cimetropium bromide, isotretinoin, and ondansetron for peptic ulcers, acne, and emesis, respectively (all drugs with positive signals are detailed in Supplementary Table S1, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=242*).

Excluding the abovementioned 34 drugs from the top 200 drugs, the majority of the drugs were immunomodulatory agents, particularly for multiple sclerosis, such as glatiramer acetate, teriflunomide, mitoxantrone, and natalizumab. In addition, the remaining drugs included a large number of drugs used to treat psoriasis and rheumatoid arthritis, including ustekinumab, tocilizumab, and infliximab. Antidiabetic (*13*) and psychotropic medications, such as antidepressants (*14*), were also included.

3.5. Age distribution of included patients

Drug-induced vaginal hemorrhage was predominantly observed in women aged 18-50 years. The higher estrogen levels may predispose these women to hormone-dependent conditions. The medications administered are often antagonistic to hormones, which increase the incidence of ADEs. Additionally, the incidence of drug-induced vaginal hemorrhage was relatively high in the postmenopausal population up to the age of 70 years (Figure 5). This may be attributed to the increased prevalence of osteoporosis or oncological diseases in the elderly population. These findings indicate that certain drugs used to treat osteoporosis and tumors have a higher risk of inducing vaginal hemorrhage.

3.6. Outcomes of included patients

The majority of individuals with drug-induced vaginal hemorrhage had adopted intervention measures to prevent more severe outcomes. However, the specific prognosis of some patients remained uncertain. Among these patients, 5,231 patients were hospitalized or had an extended hospital stay, accounting for 14% of the total reported cases. Additionally, 549 patients died owing to the adverse events, accounting for 1% of the cases (Figure 6).

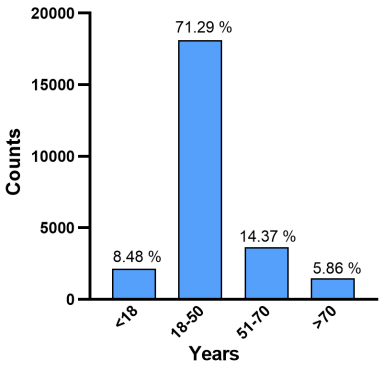

Figure 5. Age distribution of included patients. A majority of drug-induced vaginal hemorrhage cases were reported among women aged 18-50 years, which may be related to the unstable hormone levels in this age group. In addition, a relatively large proportion of pre- and post-menopausal women up to the age of 70 years had drug-induced vaginal hemorrhage, which may be related to the development of oncological diseases and osteoporosis in this age group.

4. Discussion

In this study, a comprehensive and systematic analysis was conducted on the reports of drug-induced vaginal hemorrhage in the FAERS database from 2004 to 2024. The findings provide a reference for reducing the risk of vaginal hemorrhage and promoting more rational medication use.

A total of 34 drugs, including hormonal, anticoagulant, and antifungal agents, were found to be associated with vaginal hemorrhage. Studies have shown that hormonal drugs frequently induce vaginal hemorrhage in women. However, the severity of a hemorrhage often decreases as the dosage of the drug increases. For instance, Festin *et al*. (*15*) found that the severity of initial prolonged vaginal hemorrhage experienced by patients after consuming the first 10 pills of levonorgestrel decreased with continued usage of the drug, with only a small proportion of patients (0.4%) eventually experiencing severe anemia. Similarly, Langer *et al*. (*16*) highlighted that approximately 9% of women discontinued estrogen-progestogen therapy (EPT) using conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) owing to the occurrence of vaginal hemorrhage predominantly within the first 3 months of treatment. In this study, CombiPatch, which is a combination of estrogen and progestogen, was found to be associated with vaginal hemorrhage (ROR, 20.47; 95% CI, 17.28-24.25). Hickey

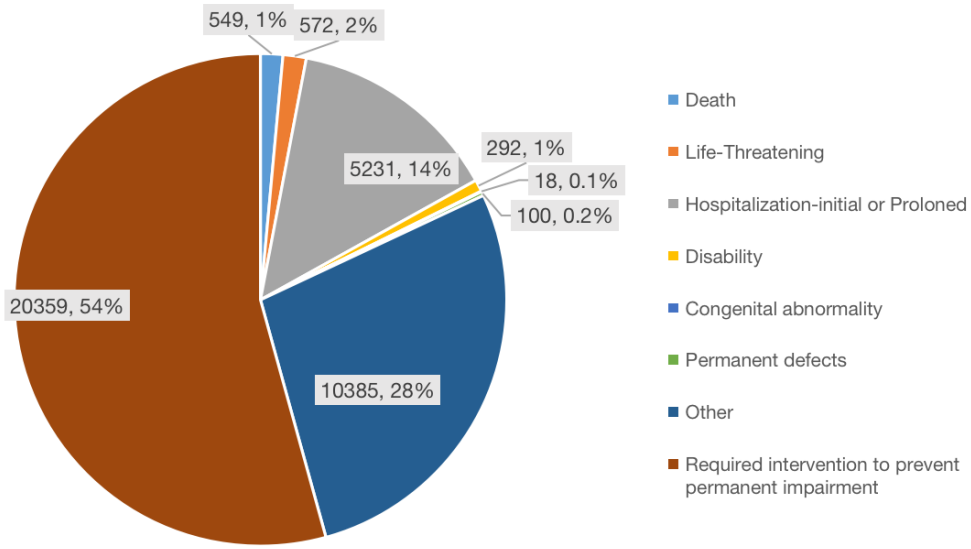

Figure 6. Outcomes of included patients. Most women with drug-induced vaginal hemorrhage had a good prognosis, with only 1% of cases resulting in deaths. The vast majority of these women were hospitalized or had a prolonged hospital stay, whereas a relatively small proportion of the women developed disability, impairment, or other complications.

(*17*) indicated that approximately 40%-60% of patients undergoing hormone therapy experienced irregular vaginal hemorrhage, which may reduce in severity with the use of low-dose estrogen.

Anticoagulant drugs are commonly associated with abnormal hemorrhage, frequently manifesting as vaginal hemorrhage in women. Anderson *et al.* (*18*) analyzed uterine hemorrhage events following oral anticoagulant use. They found a higher incidence of hemorrhage in individuals aged < 50 years than in those aged > 50 years. Huang *et al.* (*19*) showed that individuals on anticoagulant therapy experienced vaginal hemorrhage, requiring blood transfusion on the same day or gynecological surgery within 30 days were significantly more numerous than those not using anticoagulant drugs. Patel *et al.* (*9*) conducted a survey of women on anticoagulants and a control group of women not on anticoagulants. The results showed that two-thirds of women experienced heavy menstrual bleeding after initiating anticoagulant therapy, and the median duration of menstruation increased from 5 to 6 days. Compared with women in the control group, women undergoing anticoagulant therapy had significantly higher PBAC scores (representing the severity of menstrual blood loss) ($P < 0.05$) and lower quality of life scores ($P < 0.05$) (*20*).

Antifungal medications play an important role in gynecological care, particularly in the treatment of vulvovaginal candidiasis. Saghafi *et al.* (*21*) demonstrated that clotrimazole suppositories significantly alleviated itching, burning, and irritation in patients with vaginitis. Similarly, Shi *et al.* (*22*) showed that metronidazole vaginal effervescent tablets effectively reduced the levels of inflammatory markers and increased vaginal pH and cleanliness. However, it is noteworthy that antifungal drugs can strongly interact with anticoagulants, such as warfarin. Kovac *et al.* (*23*) showed that miconazole, in both oral and topical forms, significantly affected the activity of warfarin, increasing the risk of major hemorrhage events. Consequently, when anticoagulants and antifungal medications are used concurrently, the dosage of the anticoagulants should be adjusted to mitigate the risk of hemorrhage. Mechanistically, antifungal drugs can inhibit hepatic microsomal cytochrome P450 (CYP) enzymes, particularly CYP2C9, which is involved in the 7-hydroxylation of oral anticoagulants, thereby influencing the metabolism and therapeutic effects of anticoagulants.

Although the combined use of antifungal and anticoagulant drugs has been shown to increase the risk of hemorrhage, direct evidence supporting the relationship between antifungal drugs and vaginal hemorrhage is insufficient. In this study, we found that certain antifungal drugs had high positive signal values, such as miconazole (ROR, 79.42; 95% CI, 71.82-87.83) and itraconazole (ROR, 43.39; 95% CI, 30.35-62.05), with clotrimazole and sertaconazole showing similar high signal values. However, the precise relationships between these drugs and vaginal hemorrhage and the mechanisms of these drugs in inducing hemorrhage warrant further investigation.

Abnormal uterine hemorrhage is a prevalent gynecological symptom with various potential causes. The common etiological factors include endometrial polyps, adenomyosis, uterine fibroids, atypical hyperplasia of the endometrium, and endometrial cancer. Furthermore, conditions such as blood clotting disorders and polycystic ovary syndrome contribute to ovulatory dysfunction that can result in abnormal

hemorrhage. The impact of medical interventions, such as intrauterine devices, hormonal treatments, and hormone replacement therapies, and the potential side effects of certain medications, which can increase the risk of hemorrhage, should be seriously considered (*24-26*). Increased awareness and careful monitoring of drug-induced vaginal hemorrhage are crucial. Based on the findings of this study, pharmacological agents should be more judiciously used and patients should be vigilantly monitored for hemorrhages. This approach can facilitate the early detection of drug-induced hemorrhage, allowing for the adjustment of treatment plans to incorporate safer drug options, thus improving the safety and well-being of patients. These insights are invaluable for guiding rational medication practices to enhance the safety and effectiveness of medical interventions. With a comprehensive understanding and precise diagnosis of the causes of abnormal uterine hemorrhage and the availability of evidence-based treatment approaches, physicians can develop personalized treatment regimens that can not only improve the quality of life of patients but also strengthen the foundation for clinical decision-making.

In this study, "Vaginal hemorrhage" was used as the PT. According to the MedDRA hierarchical structure, this term is classified under the HLT "VULVOVAGINAL DISORDERS NEC" and the HLGT "VULVOVAGINAL DISORDERS (EXCL INFECTIONS AND INFLAMMATIONS)." Other PTs related to bleeding that are included in these HLT and HLGT categories are "COITAL BLEEDING," "VULVAL HAEMORRHAGE," "HAEMATOCOLPOS," "VAGINAL HAEMATOMA," and "VAGINAL WALL CONGESTION." Signals were detected for each of these PTs. The identified drug categories associated with these PTs were consistent with those associated with "Vaginal hemorrhage." Expanding the data to the top 1000 drugs for general screening showed that all the risk drugs identified by PT can be categorized within the existing drug classes in the current study results, with no new drug categories emerging. Notably, the positive signals for antifungal drug-induced vaginal hemorrhage were strong, warranting further investigation. This consistency further confirms the broadness and reliability of the identified drugs.

A majority of ADE reports in the FAERS database, which is a voluntary reporting system, are submitted by consumers. Therefore, the analytical findings of this study are subject to certain limitations. Despite these limitations, the findings may help improve the scrutinization of drug safety and offer critical guidance for future research into abnormal uterine hemorrhage. In addition, the findings may help develop a more judicious and safe approach to medication usage among researchers and medical practitioners, enabling the identification of latent drug-induced precipitants. This proactive approach may help decrease the risks associated with medication use and increase safety. Furthermore, the findings of this study may help strengthen clinical decision-making with robust empirical backing, improve the understanding of the causes of abnormal uterine hemorrhage, and guide the development of preventive measures for ADEs. Enhancing the safety profiles of pharmacological therapies not only benefits individualized and precise treatment but also advances the overall standard of care in medical practice.

Acknowledgements

We thank FAERS for the availability of the data. We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received October 7, 2024; Revised February 11, 2025; Accepted February 18, 2025.

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Released online in J-STAGE as advance publication February 23, 2025.