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COVID-19 vaccination and the risk of abnormal uterine bleeding: A nationwide self-controlled case series study

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ABSTRACT

Objective: To assess the association between COVID-19 vaccination and the risk of the abnormal uterine bleeding (AUB) specifically focusing on vaginal or uterine bleeding that requires hospital care in women.
Methods: We used a nationwide database in the Republic of Korea that combined COVID-19 registry data, which contains information on COVID-19 vaccination, with the claims database of the National Health Insurance Service. We included women aged 16–64 who received their first vaccine dose and were newly diagnosed with AUB in inpatient or outpatient settings within 180 days after receiving the first dose. A population-based self-controlled case series analysis was used to estimate the incidence rate ratio (IRR) during the risk periods, including 1–14, 1–21, and 1–28 days after each vaccine dose, compared to the baseline period. The baseline period was defined as the period of 1–180 days following the first vaccine dose, excluding the periods that corresponds to the risk periods. To address the SCCS assumption violation from recurrent nature, only the first event during the observation period was considered.
Results: Among 83,422 eligible patients, the risk of AUB requiring hospital care within 14 days following COVID-19 vaccination was slightly elevated compared to the baseline period (IRR 1.04, 95 % CI 1.02–1.06). The risk was notably higher after the first dose, regardless of the risk interval (14-day risk period: IRR 1.12, 95 % CI 1.09–1.15; 21-day risk period: IRR 1.08, 95 % CI 1.06–1.10; 28-day risk period: IRR 1.07, 95 % CI 1.05–1.09). No significant increase was observed after the second and third doses.
Conclusion: This study found a modest increase in healthcare utilization for AUB after the first dose of COVID-19 vaccination. However, this trend diminished with subsequent doses, showing no significantly increased risk. These findings should be interpreted while considering factors that influence healthcare-seeking behavior for unexpected vaginal or uterine bleeding.

1. Introduction

Since the introduction of COVID-19 vaccines, abnormal uterine bleeding (AUB) has been reported as one of the potential adverse events associated with the vaccines worldwide. AUB is characterized by various menstrual disturbances, including changes in regularity, frequency, duration, volume, and pattern [1]. While this condition is particularly prevalent in women during puberty and reproductive age, it can persist

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even into menopause [2]. AUB is known to be caused by various factors and is a relatively common condition, which may lead women not to reach out for medical attention for minor menstrual changes or bleeding [1]. However, in cases of unexpected abnormal vaginal or uterine bleeding unrelated to menstruation, individuals are more likely to seek medical care. AUB, which requires medical attention, can have a significant impact on the quality of life for women, causing physical discomfort and mental stress [3]. Women's menstrual conditions are influenced by various factors, such as infertility, parity, body mass index and exercise [4,5], which pose challenges for research [6]. These variabilities need to be adequately accounted for by adjusting for demographic and exposure characteristics.

After COVID-19 vaccination, numerous cases of AUB have emerged in various spontaneous adverse event reporting systems including the US Vaccine Adverse Event Reporting System, UK Medicines and Healthcare Products Regulatory Agency's Yellow Card surveillance scheme, and the Norwegian Medicines Agency [7–10]. Media reports have further highlighted cases of women experiencing increased bleeding or prolonged menopausal cycles following the vaccination. Surveys and systematic reviews conducted among women of reproductive age who received the COVID-19 vaccines have indicated that more than half of the vaccinated individuals experienced menstrual problems [11,12]. Additionally, studies utilizing mobile apps or surveys to track menstrual cycle have suggested a potential association between COVID-19 vaccination and an increase in menstrual frequency and volume [5,13–15].

Regulatory agencies in many countries have been monitoring the safety signals of AUB following COVID-19 vaccination primarily through spontaneous reporting systems. The US Centers for Disease Control and Prevention leverages a smartphone-based active monitoring system, called V-Safe, to get reports on excessive menstruation or vaginal bleeding in adult women [16]. In New Zealand, cases reported to the Center for Adverse Reactions Monitoring undergo careful review [9]. However, since it is not sufficient to solely rely on reporting database to examine the association between COVID-19 vaccination and AUB, continuous monitoring has been performed in a parallel manner. In contrast, European countries analyzed the cases reported in EudraVigilance and requested marketing authorization holders to conduct clinical evaluations and literature reviews on the cases of heavy menstrual bleeding after COVID-19 vaccination. The cases were then deliberated by the Pharmacovigilance Risk Assessment Committee, which came up with the recommendations to indicate heavy menstrual bleeding as a possible side effect in the product information for mRNA COVID-19 vaccines [17–19]. Despite existing studies based on questionnaires and reported data, there is still a lack of real-world evidence to confirm the association between COVID-19 vaccination and the risk of AUB. Additionally, in the context of mass COVID-19 vaccination, there has been limited research addressing such complexities due to challenges in securing a highly comparable unvaccinated group. In this context, the self-controlled case series (SCCS) method, originally developed for vaccine safety assessment, was useful in addressing the above limitations.

The objective of this study is to evaluate the risk of AUB following COVID-19 vaccination, specifically vaginal or uterine bleeding requiring hospital visit, in women who received COVID-19 vaccination after February 26, 2021, when the first COVID-19 vaccination started in South Korea. To address existing limitations, we employed a SCCS design using a nationwide database.

2. Materials and methods

2.1. Data sources

We used a nationwide database that linked the COVID-19 registry managed by the Korea Disease Control and Prevention Agency (KDCA) and claims data collected by the National Health Insurance Service (NHIS). The KDCA's registry contains COVID-19 diagnosis information, such as the date of confirmed COVID-19 infection, as well as COVID-19 vaccination data, including vaccination date, vaccine type and vaccine dosage for all citizens [20]. The claims data offers demographic and diagnostic information, as well as procedures, and prescription records of all individuals enrolled in the national health insurance system, which covers the entire population of 51 million citizens in the Republic of Korea [21]. The data utilized for this study were collected between January 1, 2002, and September 30, 2022. The two databases were linked by NHIS based on resident registration number and provided to us in a de-identified format.

2.2. Study design and inclusion criteria

We used a population-based SCCS method to assess the safety of COVID-19 vaccines regarding the potential risk of AUB. SCCS is a case-only design that offers certain advantages. It does not require separate controls but implicitly controls for any fixed confounders [22,23]. In this design, the incidence of the outcome during the exposed risk period is compared to that of the "unexposed" baseline period for the same individual [22]. The SCCS design works particularly well when there is difficulty in identifying a suitable non-exposure control group. This is often the case when a significant portion of the population experiences the exposure, as with the case of the COVID-19 vaccine [22]. Several key assumptions have to be satisfied when using the SCCS design: (1) the study outcome must be recurrent and independent, or if it is unique, it should be uncommon; (2) the likelihood of exposure should not be affected by the occurrence of an event; and (3) the occurrence of an event should not influence the premature termination of the observation period due to death [24,25]. Due to its nature, AUB can recur repeatedly; however, this can be addressed by considering only the initial events [22]. Given the recurrent nature of AUB events and the likelihood of follow-up visits that may increase the probability of subsequent episodes, only the first event within the observation period was considered as the outcome of interest. AUB is a condition characterized by relatively mild symptoms that do not require discontinuation of the vaccination or pose a risk of death on its own.

The target population for our study was women aged 16 to 64 who received their first dose of the COVID-19 vaccine between February 26, 2021, and April 3, 2022. Each participant was ensured a complete follow-up period. The study focused on individuals who were diagnosed with AUB within a 180-day observation period after receiving their first dose of COVID-19 vaccine. We only used the post-vaccination observation period to minimize bias arising from the depletion or enrichment of adverse events in the pre-vaccination period. The appendix presents the types of COVID-19 vaccines available in Korea during the study period (Table S1). People who had incomplete or inaccurate vaccination records were excluded from the study.

The primary outcome of the study was the AUB requiring a healthcare visit. The outcome was defined using the International Classification of Diseases, 10th revisions (ICD-10) diagnosis codes and procedure or surgery codes (Table S2). Patients with a principal diagnosis of vaginal or uterine bleeding including menorrhagia and metrorrhagia (ICD-10 codes: N92.2, N92.4, N93.8, N93.9, or N95.0) in either outpatient or inpatient settings during the observation period, who underwent a related procedure or surgery within 7 days before or after the diagnosis, were identified. Only the date of the first diagnosis during the study period was considered. We excluded those who had a pre-existing diagnosis of AUB, structural causes of AUB based on the International Federation of Gynecology and Obstetrics classification system [26], or cancer within a year prior to the AUB diagnosis. Patients who had a history of hemorrhagic or genetic disorder, platelet dysfunction or thrombocytopenia, liver disease or cirrhosis, or organ transplant between January 1, 2002, and the AUB diagnosis date were also excluded. Additionally, pregnant women between the first vaccination date and the AUB diagnosis were excluded (Table S3).

We predefined the risk periods as 14, 21, and 28 days after each

vaccination dose. These periods were selected to account for menstrual cycles and to focus on bleeding events that necessitate healthcare visits which occur before the onset of the next menstrual period. The duration of the risk windows was based on the assumption that AUB may occur acutely in response to immune activation following vaccination, considering biologically plausible mechanisms associated with short-term post-vaccination immune responses. Following vaccination, acute immune activation—including cytokine release and T-cell activation—typically occurs within days to weeks. These processes drive antibody production and are generally most pronounced during the first two to three weeks post-vaccination [27,28]. As discussed later, these immunologic events may cause temporary disruption of the hypothalamic-pituitary-gonadal axis, potentially leading to menstrual irregularities or bleeding. Based on these considerations, we determined that the first 28 days following vaccination represented the most biologically plausible window to capture acute-onset AUB events.

The baseline period spanned from 1 to 180 days following the first dose, excluding the period that overlapped with the risk period. If a subsequent vaccine dose was administered during the risk period, the risk period of the prior dose would end on the day of that subsequent vaccination and the risk period for that subsequent dose would be calculated starting from the next day of its administration. The observation period ended at the earliest of either the date of death or 180 days after receiving the first COVID-19 vaccination (Fig. S1).

2.3. Statistical analysis

We described the characteristics of the study participants, who were diagnosed with AUB after receiving the COVID-19 vaccine. Only the first recorded diagnosis of an AUB event during the observation period was included in the analysis. We examined their age, months since the first vaccination, health insurance type, type of COVID-19 vaccine received for each dose, the number of doses received prior to the initial AUB event, and the Charlson comorbidity index score. To estimate the incidence rate ratios (IRRs) and 95 % confidence intervals (CIs) comparing the relative incidence rate of AUB during the risk and the baseline periods, an SCCS design using a conditional Poisson regression model was employed. Given the relatively short observation period, we did not adjust for time-varying confounders such as age and seasons. To investigate the dependence of the results on covariates, we conducted subgroup analyses by age groups and by vaccine products administered before the incidence of AUB event (BNT162b2, ChAdOx1, mRNA-1273, Ad26.COV2·S, or NVX-CoV2373). Two sensitivity analyses were conducted. The first refined the eligibility criteria to exclude only individuals with a medical history of specific diseases such as AUB, endometrial hyperplasia, cancer, hemorrhagic disorder, or genetic disorder, or those who were pregnant at the time of vaccination. The second excluded individuals with a history of SARS-CoV-2 infection within 28 days prior to the AUB event to account for the potential effects of infection. All data management and statistical analyses were conducted using SAS Enterprise Guide 8.2 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

The demographic and vaccination characteristics of 16,074,504 women aged 16–64 who received their first COVID-19 vaccine were shown in the Table S4. During the study period, 15,911,880 (99.0 %) subjects were vaccinated for two doses and 11,266,864 (70.1 %) for three doses. Of the 1,039,895 patients diagnosed with uterine and vaginal bleeding-related conditions between February 27, 2021, and September 30, 2022, a total of 83,422 people had a diagnosis of AUB during the observation period. After excluding cases that occurred on the vaccination day outside the risk periods, 82,214 patients were included in the analysis with a 14-day risk period, 82,301 with a 21-day risk period, and 82,400 with a 28-day risk period (Fig. 1).

Table 1 presents the demographic and vaccination characteristics of patients who experienced AUB and sought healthcare services. The number of patients with cases occurring in both the risk and baseline periods is shown according to the length of each risk period.

3.2. Risk for vaginal or uterine bleeding

Fig. 2 presents the results of the SCCS analysis on the risk of AUB requiring hospital care following COVID-19 vaccination. The analysis detected an increased risk of AUB events within the 14-day risk period following COVID-19 vaccination compared to the baseline period (IRR 1.04, 95 % CI 1.02–1.06). For the longer risk periods, the results were not statistically significant (21-day risk period: IRR 1.01, 95 % CI 1.00–1.03; 28-day risk period: IRR 1.01, 95 % CI 0.99–1.02).

Dose-specific analysis indicated a statistically significant increase in the risk of AUB after the first dose across all risk periods (14-day risk period: IRR 1.12, 95 % CI 1.09–1.15; 21-day risk period: IRR 1.08, 95 % CI 1.06–1.10; 28-day risk period: IRR 1.07, 95 % CI 1.05–1.09). However, for the second and third doses, the IRR estimates were either not statistically significant or reduced.

3.3. Sensitivity analysis

We obtained similar results in the sensitivity analyses. Among 111,561 subjects for sensitivity analysis with modified exclusion criteria, 109,947 patients were included in the analysis with a 14-day risk period, 110,073 with a 21-day risk period, and 110,212 with a 28-day risk period after excluding cases that occurred on the vaccination day outside the defined risk periods (Table S5). The risk of AUB requiring medical attention exhibited a modest but statistically significant increase during the risk period compared to the baseline (14-day risk period: IRR 1.05, 95 % CI 1.04–1.07; 21-day risk period: IRR 1.02, 95 % CI 1.01–1.04; 28-day risk period: IRR 1.01, 95 % CI 1.00–1.03). Consistent with the primary analysis, dose-specific analysis revealed a statistically significant increase in the risk of AUB following the first dose across all risk periods, whereas for the second and third doses, IRR estimates were either reduced or not statistically significant (Fig. S2). For the sensitivity analysis excluding individuals with prior SARS-CoV-2 infection, 82,684 out of 83,422 subjects (99.1 %) were included in the analysis. As the number of subjects was nearly identical to that of the primary analysis, the results were also highly comparable (Table S6).

3.4. Subgroup analysis

Fig. 3 and Fig. 4 present the results of subgroup analyses by age group and vaccine product prior to the initial AUB event, respectively. The age-based subgroup analysis using a 14-day risk period showed an increased risk of AUB across all age groups except for the 60–64 age bracket. However, for the 21-day and 28-day risk periods, a significant risk was observed only in the 40–49 and 50–59 age groups. In the dose-specific analysis, an increased risk of AUB requiring hospital care after the first dose was observed across all age groups except for those aged 60–64 years, whereas most age groups did not exhibit an increased risk following the second or third doses. Similar results were found in subgroup analyses that applied modified exclusion criteria for sensitivity analysis (Fig. S3).

In the subgroup analysis by vaccine type administered before diagnosis, an elevated risk was observed after the first dose across all vaccines except for NVX-CoV2373. The estimates were higher for non-replicating viral vector platform vaccines compared to mRNA platform vaccines. The highest IRR for AUB was observed in those receiving the ChAdOx1 vaccine for the first dose. When sensitivity criteria were applied, a higher risk following the first dose was observed across all vaccine types, including NVX-CoV2373 (Fig. S4).

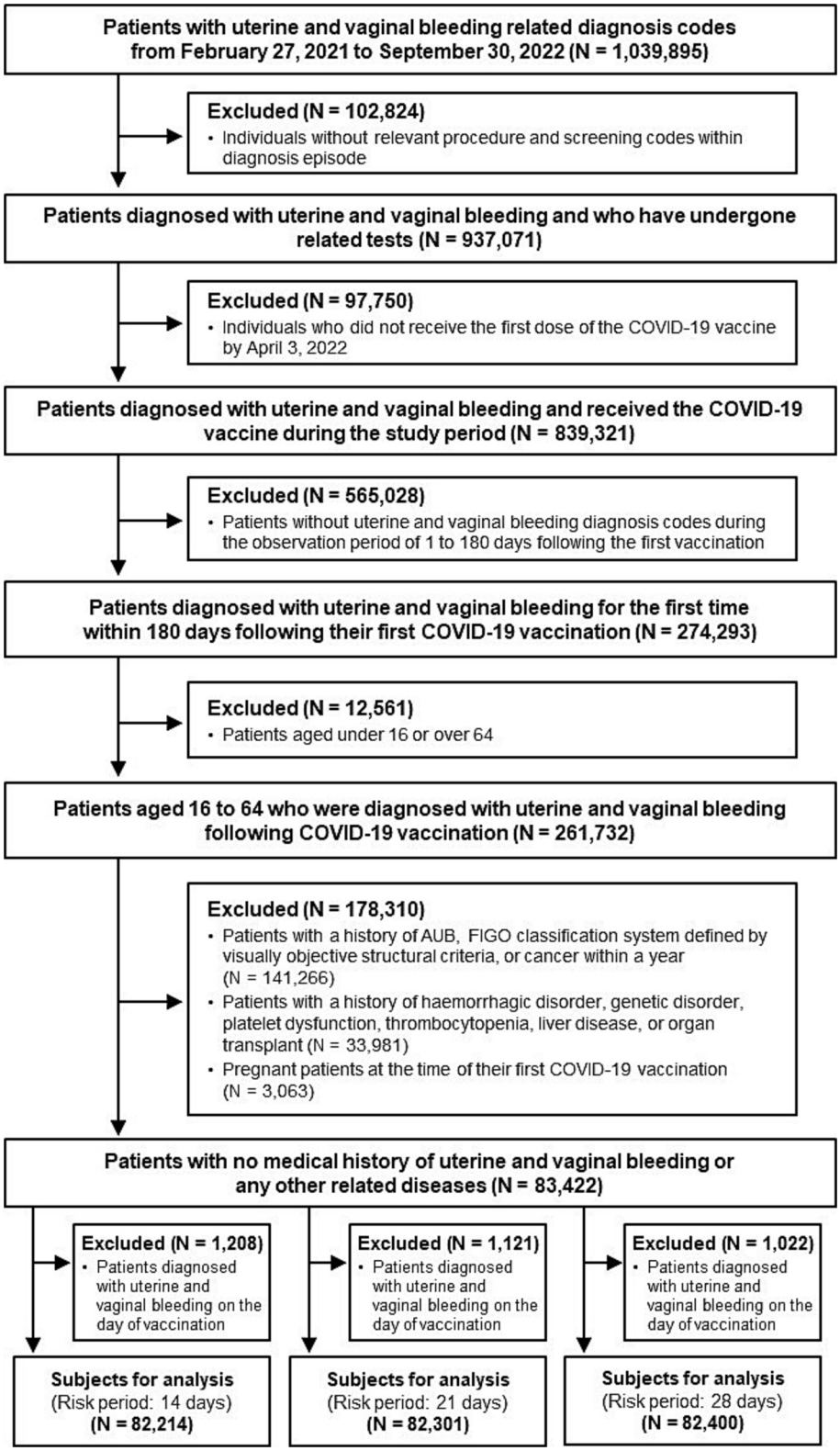


Fig. 1. Flowchart of study population selection.

4. Discussion

4.1. Main findings

This large population-based SCCS study assessed the risk of healthcare contacts for AUB following COVID-19 vaccination in women in Korea. We found a modest increase in the risk of vaginal or uterine bleeding that require hospital care within 28 days after the first COVID-19 vaccination. However, this risk was not elevated for subsequent doses. The findings were consistent regardless of the age groups, except for those aged 60–64. The risk of hospital visits due to AUB was higher when the most recently administered vaccine was ChAdOx1. These

Table 1
Baseline characteristics of patients who received COVID-19 vaccination and had a diagnosis of AUB in the risk or baseline periods for self-controlled case series analysis.

	14 days		21 days		28 days	
	Cases in risk period	Cases in baseline period	Cases in risk period	Cases in baseline period	Cases in risk period	Cases in baseline period
Total	15,077	67,137	22,499	59,802	29,446	52,954
Age at first vaginal or uterine diagnosis (years), n (%)						
Mean ± SD	36.9 ± 12.0	36.6 ± 12.0	37.0 ± 12.0	36.5 ± 11.9	37.0 ± 12.0	36.4 ± 11.9
16–29	5318 (35.3)	24,147 (36.0)	7851 (34.9)	21,653 (36.2)	10,236 (34.8)	19,314 (36.5)
30–39	3434 (22.8)	15,980 (23.8)	5109 (22.7)	14,331 (24.0)	6738 (22.9)	12,725 (24.0)
40–49	3518 (23.3)	15,191 (22.6)	5304 (23.6)	13,417 (22.4)	6949 (23.6)	11,797 (22.3)
50–59	2399 (15.9)	9573 (14.3)	3622 (16.1)	8360 (14.0)	4699 (16.0)	7288 (13.8)
60–64	408 (2.7)	2246 (3.3)	613 (2.7)	2041 (3.4)	824 (2.8)	1830 (3.5)
Diagnosis setting, n (%)						
Inpatient	54 (0.4)	216 (0.3)	88 (0.4)	182 (0.3)	113 (0.4)	157 (0.3)
Outpatient	15,023 (99.6)	66,921 (99.7)	22,411 (99.6)	59,620 (99.7)	29,333 (99.6)	52,797 (99.7)
Insurance type, n (%)						
Health insurance	14,840 (98.4)	66,179 (98.6)	22,155 (98.5)	58,949 (98.6)	28,995 (98.5)	52,204 (98.6)
Medical aid	237 (1.6)	958 (1.4)	344 (1.5)	853 (1.4)	451 (1.5)	750 (1.4)
Vaccine type (first dose), n (%)						
BNT162b2	10,286 (68.2)	44,320 (66.0)	15,361 (68.3)	39,329 (65.8)	19,953 (67.8)	34,794 (65.7)
ChAdOx1	1659 (11.0)	8914 (13.3)	2492 (11.1)	8081 (13.5)	3301 (11.2)	7272 (13.7)
mRNA-1273	2972 (19.7)	12,968 (19.3)	4419 (19.6)	11,521 (19.3)	5910 (20.1)	10,072 (19.0)
Ad26.COV2·S	140 (0.9)	758 (1.1)	189 (0.8)	709 (1.2)	240 (0.8)	658 (1.2)
NVX-CoV2373	20 (0.1)	177 (0.3)	38 (0.2)	162 (0.3)	42 (0.1)	158 (0.3)
Vaccine type (second dose), n (%)*						
BNT162b2	11,063 (73.4)	48,090 (71.6)	16,507 (73.4)	42,730 (71.5)	21,454 (72.9)	37,840 (71.5)
ChAdOx1	871 (5.8)	4778 (7.1)	1328 (5.9)	4321 (7.2)	1752 (5.9)	3897 (7.4)
mRNA-1273	2983 (19.8)	12,876 (19.2)	4412 (19.6)	11,447 (19.1)	5894 (20.0)	10,007 (18.9)
Ad26.COV2·S	3 (0.0)	7 (0.0)	4 (0.0)	6 (0.0)	4 (0.0)	6 (0.0)
NVX-CoV2373	18 (0.1)	130 (0.2)	37 (0.2)	114 (0.2)	43 (0.1)	108 (0.2)
Vaccine type (third dose), n (%)						
BNT162b2	6272 (41.6)	21,796 (32.5)	9333 (41.5)	18,778 (31.4)	12,126 (41.2)	16,015 (30.2)
ChAdOx1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
mRNA-1273	1622 (10.8)	5481 (8.2)	2421 (10.8)	4682 (7.8)	3188 (10.8)	3934 (7.4)
Ad26.COV2·S	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NVX-CoV2373	10 (0.1)	40 (0.1)	16 (0.1)	34 (0.1)	19 (0.1)	31 (0.1)
Vaccine product immediately preceding to initial vaginal or uterine code, n (%)						
BNT162b2	10,731 (71.2)	47,022 (70.0)	16,019 (71.2)	41,818 (69.9)	20,817 (70.7)	37,077 (70.0)
ChAdOx1	1272 (8.4)	6460 (9.6)	1907 (8.5)	5825 (9.7)	2529 (8.6)	5203 (9.8)
mRNA-1273	2961 (19.6)	12,776 (19.0)	4405 (19.6)	11,332 (18.9)	5889 (20.0)	9890 (18.7)
Ad26.COV2·S	93 (0.6)	696 (1.0)	129 (0.6)	660 (1.1)	167 (21.2)	622 (1.2)
NVX-CoV2373	20 (0.1)	183 (0.3)	39 (0.2)	167 (0.3)	44 (0.1)	162 (0.3)
Charlson comorbidity index score, n (%)						
0	12,292 (81.5)	54,834 (81.7)	18,316 (81.4)	48,891 (81.8)	23,913 (81.2)	43,380 (81.9)
1–4	2729 (18.1)	12,064 (18.0)	4096 (18.2)	10,703 (17.9)	5421 (18.4)	9390 (17.7)
+ 5	56 (0.4)	239 (0.4)	87 (0.4)	208 (0.3)	112 (0.4)	184 (0.3)
Comorbidities, n (%)						
Myocardial infarction	18 (0.1)	71 (0.1)	25 (0.1)	64 (0.1)	31 (0.1)	58 (0.1)
Congestive heart failure	68 (0.5)	366 (0.5)	108 (0.5)	326 (0.5)	135 (0.5)	299 (0.6)
Peripheral vascular disease	459 (3.0)	2070 (3.1)	704 (3.1)	1825 (3.1)	907 (3.1)	1625 (3.1)
Cerebrovascular disease	108 (0.7)	548 (0.8)	180 (0.8)	476 (0.8)	250 (0.8)	408 (0.8)
Dementia	41 (0.3)	179 (0.3)	62 (0.3)	158 (0.3)	74 (0.3)	146 (0.3)
Chronic pulmonary disease	446 (3.0)	2035 (3.0)	676 (3.0)	1806 (3.0)	884 (3.0)	1599 (3.0)
Connective tissue disease	129 (0.9)	612 (0.9)	200 (0.9)	541 (0.9)	270 (0.9)	472 (0.9)
Peptic ulcer disease	534 (3.5)	2188 (3.3)	772 (3.4)	1952 (3.3)	1012 (3.4)	1714 (3.2)
Hepatic disease	1226 (8.1)	5377 (8.0)	1863 (8.3)	4743 (7.9)	2464 (8.4)	4147 (7.8)
Diabetes mellitus	891 (5.9)	3862 (5.8)	1332 (5.9)	3422 (5.7)	1766 (6.0)	2992 (5.7)
Hemiplegia	13 (0.1)	50 (0.1)	22 (0.1)	41 (0.1)	26 (0.1)	37 (0.1)
Renal disease	29 (0.2)	90 (0.1)	37 (0.2)	82 (0.1)	47 (0.2)	74 (0.1)
HIV infection	0 (0.0)	7 (0.0)	0 (0.0)	7 (0.0)	1 (0.0)	6 (0.0)

Abbreviation: AUB, Abnormal uterine bleeding; SD, Standard deviation; HIV, Human immunodeficiency virus.

* The study included individuals who had received at least the first dose of the COVID-19 vaccine. Therefore, individuals who had not received the second or third dose were included in the analysis. The percentage of vaccine types was calculated based on the total number of patients included in the study.

	Risk period	Events	Incidence rate	Incidence rate ratio (95% confidence interval)
14 days	Baseline period	67,137	2.09	1.00
	Overall	15,077	2.17	1.04 (1.02–1.06)
	First dose	6,842	2.34	1.12 (1.09–1.15)
	Second dose	5,948	2.07	0.99 (0.97–1.02)
	Third dose	2,287	1.99	0.95 (0.91–0.99)
21 days	Baseline period	59,802	2.09	1.00
	Overall	22,499	2.12	1.01 (1.00–1.03)
	First dose	10,170	2.26	1.08 (1.06–1.10)
	Second dose	9,022	2.04	0.98 (0.96–1.00)
	Third dose	3,307	1.95	0.93 (0.90–0.96)
28 days	Baseline period	52,954	2.09	1.00
	Overall	29,446	2.10	1.01 (0.99–1.02)
	First dose	13,038	2.23	1.07 (1.05–1.09)
	Second dose	12,161	2.04	0.98 (0.96–0.99)
	Third dose	4,247	1.94	0.93 (0.90–0.96)



Fig. 2. Risk of vaginal or uterine bleeding following COVID-19 vaccination in self-controlled case series.

Subgroup	Dose	Incidence rate ratio (95% confidence interval) Risk period 14 days	21 days	28 days
16-29	Overall	1.03 (1.00–1.06)	0.98 (0.96–1.01)	0.98 (0.96–1.01)
	First dose	1.10 (1.06–1.15)	1.04 (1.01–1.08)	1.04 (1.01–1.08)
	Second dose	0.97 (0.93–1.01)	0.94 (0.90–0.98)	0.94 (0.91–0.97)
	Third dose	0.97 (0.91–1.04)	0.94 (0.89–0.99)	0.95 (0.90–1.00)
30-39	Overall	1.04 (1.00–1.08)	1.00 (0.97–1.04)	1.00 (0.97–1.03)
	First dose	1.12 (1.06–1.17)	1.06 (1.01–1.11)	1.05 (1.01–1.09)
	Second dose	0.98 (0.92–1.03)	0.96 (0.92–1.01)	0.98 (0.94–1.02)
	Third dose	0.97 (0.89–1.06)	0.95 (0.88–1.02)	0.95 (0.88–1.01)
40-49	Overall	1.05 (1.01–1.09)	1.04 (1.01–1.07)	1.04 (1.01–1.07)
	First dose	1.15 (1.09–1.21)	1.13 (1.08–1.18)	1.12 (1.07–1.16)
	Second dose	1.01 (0.96–1.07)	1.00 (0.96–1.05)	1.01 (0.97–1.05)
	Third dose	0.91 (0.84–0.99)	0.91 (0.85–0.98)	0.91 (0.85–0.96)
50-59	Overall	1.07 (1.03–1.12)	1.07 (1.03–1.11)	1.04 (1.00–1.08)
	First dose	1.16 (1.09–1.24)	1.15 (1.09–1.21)	1.11 (1.06–1.17)
	Second dose	1.06 (0.99–1.13)	1.06 (1.01–1.12)	1.03 (0.98–1.08)
	Third dose	0.94 (0.86–1.03)	0.93 (0.86–1.01)	0.93 (0.87–0.99)
60-64	Overall	0.96 (0.87–1.07)	0.94 (0.86–1.03)	0.94 (0.87–1.02)
	First dose	0.98 (0.84–1.13)	0.97 (0.86–1.09)	0.95 (0.86–1.06)
	Second dose	0.95 (0.82–1.10)	0.91 (0.80–1.03)	0.93 (0.84–1.04)
	Third dose	0.99 (0.69–1.42)	0.90 (0.66–1.23)	0.87 (0.66–1.15)

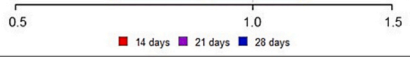


Fig. 3. Subgroup analysis by age group for the risk of vaginal or uterine bleeding following COVID-19 vaccination in self-controlled case series analysis.

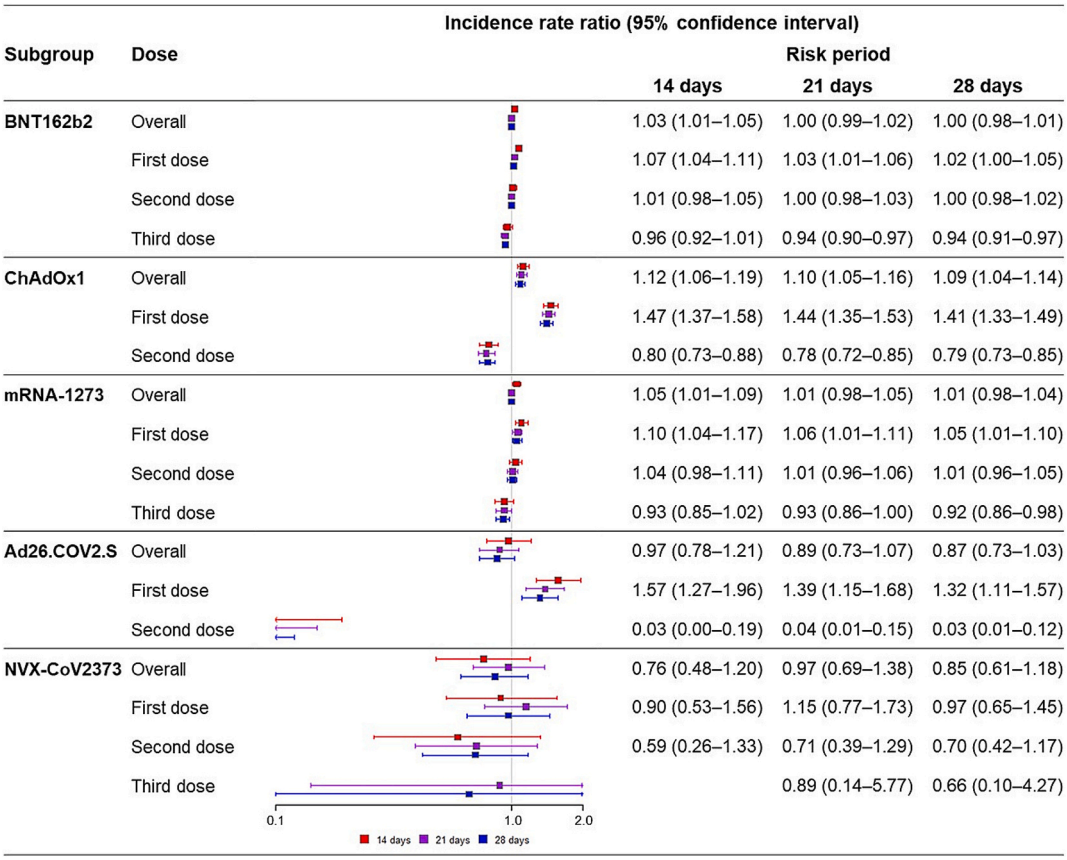


Fig. 4. Subgroup analysis by previous vaccine product type group for the risk of vaginal or uterine bleeding following COVID-19 vaccination in self-controlled case series analysis.

trends were similarly observed in sensitivity analyses with relaxed exclusion criteria.

4.2. *Comparison of study findings with existing literature*

Several findings on menstrual disturbances or bleeding have suggested a potential association between COVID-19 vaccination and heavy or prolonged bleeding [5,7–18]. The findings of this study align with previous researches indicating a potential increase in the risk of heavy menstrual bleeding following COVID-19 vaccination [5,29–32]. Previous studies have also found that such bleeding issues tend to disappear within months post-vaccination [31,33]. In particular, we have found the risk of heavy or prolonged bleeding tend to spike after the first dose but decrease with subsequent doses, as these bleeding episodes generally resolve over time. Despite an increase in medical visits for AUB following the first dose, no significant risk was observed for the second and third doses. These results suggest that while COVID-19 vaccination may transiently elevate risks associated with AUB, the effects are temporary. However, some observational studies have not found a significant association between COVID-19 vaccination and AUB. For example, a study using data from the Kaiser Permanente Northwest, a VSD site, reported no significant difference in healthcare visits for AUB before and after COVID-19 vaccination [34]. Another study using linked data from Swedish national and regional registers observed a slight increase in the risk of postmenopausal bleeding or menstrual disturbances requiring hospital visits following COVID-19 vaccination but found no significant risk for premenopausal bleeding [35]. Notably, the study also found a 14 % increase in risk within 1–7 days following the first dose, though this result was not statistically significant. The study evaluated premenstrual bleeding risk within 8–90 days post-vaccination, whereas our study focused on unexpected bleeding risk within a shorter time frame. This difference in methodology may partially explain the discrepancies in our findings.

To assess the association between COVID-19 vaccination and AUB, including vaginal or uterine bleeding, various study designs have been employed with diverse data sources across different countries. These include large population-based registries, web-based questionnaires, cohort studies comparing risks between vaccinated and unvaccinated individuals [35], case-control studies [30,36], and SCCS designs to control time-invariant factors, as shown in the Norwegian studies [5,29]. The variability in previous study results may stem from such diversity of data sources and designs, especially given the challenge of estimating outcomes influenced by menstrual cycle timing post-exposure. Our study employed the SCCS design to address potential issues of comparability between exposure and control groups in a highly vaccinated population and to minimize the influence of unobserved time-invariant factors. We focused specifically on abnormal vaginal or uterine bleeding across various risk periods within the first cycle following vaccination.

4.3. *Interpretation*

Due to the limited number of biological studies exploring AUB in association with vaccination, the underlying mechanism explaining the relationship between COVID-19 vaccination and AUB remains unclear. However, as the menstrual cycle involves an intricate interaction among various hormones, tissues, and organ systems [37], it is susceptible to influences from various factors, such as viral infections and alterations in lifestyle.

The physiological response to SARS-CoV-2 infection can involve excessive immune activation, potentially leading to a cytokine storm [38,39]. Additionally, SARS-CoV-2 may directly affect reproductive

function by binding to angiotensin-converting enzyme 2 receptors, which are highly expressed in the ovaries, thereby potentially contributing to AUB [40]. In contrast, following COVID-19 vaccination, the immune response activates leukocytes and T lymphocytes to produce antibodies against the virus [41,42]. This vaccine-induced immune activity may temporarily influence the hypothalamic-pituitary-gonadal axis due to a redistribution of energy resources and immune-mediated stress responses [37,39], potentially leading to short-term menstrual irregularities. The underlying mechanisms for the risk of uterine or vaginal bleeding based on vaccine platform type remain unclear. Given the predominance of prior research focusing on the more widely administered mRNA platform vaccines globally, further investigation is warranted to determine if there is a stronger association between non-replicating viral vector platforms and AUB.

This study focused on short-term AUB following COVID-19 vaccination, specifically abnormal vaginal or uterine bleeding and excessive menstruation. Therefore, changes in menstrual cycle length or regularity were not analyzed. Since such outcomes may be influenced over a longer period by the physiological and pharmacological effects of vaccine-induced antibodies, further research using study designs more appropriate for assessing longer-term outcomes would be necessary to explore these effects.

When interpreting our results, it is important to consider how unexpected AUB might influence healthcare-seeking behaviors. Since these types of bleeding are generally not life-threatening, some patients may choose not to seek medical care [43]. Previous studies have indicated that even among women experiencing heavy menstrual bleeding, 40 % of them do not consult with healthcare professionals, and more than half receive no diagnosis or treatment [44]. As a result, healthcare services are often sought only for more severe symptoms. As our study focused on hospital visits, it likely captured cases with severe or unexpected bleeding, which may explain the variability in dose-specific IRRs. Anxiety related to vaccination may have also prompted initial medical visits, potentially influencing our findings. While various factors affecting healthcare visits cannot be ruled out, numerous studies have reported a range of menstrual disorders, including vaginal or uterine bleeding, suggesting a possible association with COVID-19 vaccination. Additionally, the relatively lower AUB risk observed after the second and third doses compared to the first dose may be influenced by a potential bias introduced by including only the first event during the observation period. This bias is related to the cumulative incidence and the distribution of risk periods, whereby later doses are less likely to have the first event occur in the risk periods, potentially leading to an underestimation of the relative incidence associated with these exposures [45]. Further research is needed to explore how post-vaccination bleeding affects the patterns of healthcare visits, treatment needs, and quality of life.

4.4. Strengths and limitations

The database we used for the study encompasses the entire Korean population and includes all patients diagnosed with AUB who received the COVID-19 vaccine at least once. Thus, our findings provide robust insights into a large population within a real-world setting. We utilized an SCCS design to implicitly adjust for time-invariant confounders by comparing the risk period and the baseline for the same individual. Given that AUB is greatly influenced by individual characteristics, the SCCS design could be useful in controlling unmeasured confounding factors.

Yet, our study has several limitations. Firstly, we relied on ICD-10 diagnostic codes along with codes for screening tests and procedures to establish an operational definition for identifying AUB patients from health insurance claims data. While the codes for screening and procedures are typically used to claim national health insurance benefits, it is possible that some patients who did not meet the operational definition were overlooked. Secondly, as we used insurance claims data, our study focused on AUB cases only with hospital visits. This may introduce a potential bias towards more severe or clinically significant cases, as patients with minor events who did not seek medical attention would not be included in the study. Therefore, the prevalence of milder cases might be underestimated. Thirdly, the timing of AUB occurrence and subsequent hospital visits recorded in the claims data can vary depending on individuals and the severity of symptoms. The claims data also included AUB cases with different durations from temporary to prolonged cases. Fourthly, only the first AUB event was included in this study to address potential event dependence, which may otherwise violate a key assumption of the SCCS design. While this approach is generally recommended to mitigate event dependence, it may have led to underestimation of risk following the second or third doses if these later doses were indeed associated with elevated AUB risk. Lastly, this study focused only on evaluating the risk of AUB developed within a relatively short risk period following vaccination. For this reason, further investigations are warranted to explore the association between COVID-19 vaccination and AUB in relation to menstrual cycle and volume, as well as to examine more closely the population affected by prolonged bleeding subsequent to COVID-19 vaccination.

5. Conclusion

In conclusion, this study observed a slight increase in healthcare utilization for AUB within the first month following the initial dose of the COVID-19 vaccine. However, an attenuating trend was observed with subsequent doses. Our study utilized a nationwide linked-data to provide evidence on the risk of vaginal or uterine bleeding after COVID-19 vaccination, contributing to the enhancement of vaccine safety information. These findings should be interpreted by taking into account factors that can affect healthcare-seeking behaviors and patterns of medical visits for unexpected AUB.

Authors contribution

N.Y.J. and S.C. are joint first authors. J.S·P. and N.K.C. are joint corresponding authors. All authors were involved in the conceptualizing and design of the study. N.Y.J. and E.L. conducted the statistical analyses, had full access to the data, and take responsibility of the accuracy of the data analysis. S.C., J.R.L., J.Y.S., and J.S.P. interpreted the data. N.Y.J., S.C., and N.K.C. wrote the first draft. All authors contributed to the interpretation of the analysis, critically reviewed the manuscript, and approved the final version of the manuscript. All authors had final responsibility for the decision to submit for publication. J.S.P and N.K.C. are guarantors.

CRediT authorship contribution statement

Na-Young Jeong: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **SiHyun Cho:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Eunsun Lim:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Jung Ryeol Lee:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Jae Yen Song:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Joong Shin Park:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Nam-Kyong Choi:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Ethics statement

This study was conducted in agreement with the Declaration of Helsinki and approved by the Public Institutional Review Board Designated by Ministry of Health and Welfare of the Republic of Korea

(P01–202203–01-005). Informed consent was not required due to the utilization of anonymized patient data.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nam-Kyong Choi reports financial support was provided by Korea Disease Control and Prevention Agency. Na-Young Jeong reports financial support was provided by Korea Disease Control and Prevention Agency. Eunsun Lim reports financial support was provided by Korea Disease Control and Prevention Agency. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127619.

Data availability

The study utilized pseudonymized patient-level data from Korea Disease Control and Prevention Agency and National Health Insurance Service, which is protected by strict confidentiality under the Personal Information Protection Act. Access to personal data is granted solely for research purposes by the responsible authority upon submission of a former application.

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