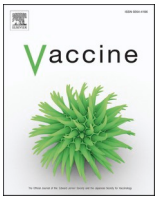
Vaccine 42 (2024) 126252

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Risk of heavy menstrual bleeding following COVID-19 vaccination: A nationwide case-control study

Jérémie Botton [a,b,*], Marion Bertrand [a], Marie-Joëlle Jabagi [a], Lise Duranteau [c], Kim Bouillon [a], Jérôme Drouin [a], Laura Semenzato [a], Stéphane Le Vu [a], Alain Weill [a], Mahmoud Zureik [a,d], Rosemary Dray-Spira [a]

[a] EPIPHARE Scientific Interest Group in Epidemiology of Health Products (French National Agency for the Safety of Medicines and Health Products - ANSM, French National Health Insurance - CNAM), Saint-Denis, France
[b] Université Paris-Saclay, Faculté de pharmacie, Orsay 91400, France
[c] Department of Medical Gynecology, Bicêtre Hospital, AP.HP University Paris-Saclay, 94270 Le Kremlin Bicêtre, France
[d] University Paris-Saclay, UVSQ, University Paris-Sud, Inserm, Anti-infective evasion and pharmacoepidemiology, CESP, Montigny le Bretonneux, France

ARTICLE INFO

Keywords:
COVID-19 vaccine
Heavy menstrual bleeding
Vaccine
Women

ABSTRACT

Background: COVID-19 vaccination has been inconsistently associated with an increased risk of heavy menstrual bleeding in previous studies. This study aimed to assess the risk of heavy menstrual bleeding requiring hospital care following COVID-19 vaccination according to the number of doses received and the time elapsed since vaccination.

Methods: Using comprehensive data of the French National Health Data System, we carried out a case-control study. Non-pregnant 15–50 years old women who had a hospital discharge diagnosis of heavy menstrual bleeding between May 12, 2021, and August 31, 2022 (cases) were randomly matched to up to 30 controls of same age, place of residence, social deprivation index, and contraceptive use profile at the date of case hospital admission (index date). Conditional logistic regression models were used to estimate the risk of hospital care for heavy menstrual bleeding associated with primary or booster doses and delay since last COVID-19 vaccination at index date, adjusting for socio-demographic characteristics, comorbidities, healthcare use indicators, and recent SARS-CoV-2 infection.

Results: A total of 4610 cases and 89,375 matched controls were included (median age, 42 years). Compared to unvaccinated women, the risk of hospital care for heavy menstrual bleeding was increased in those having received a last dose of primary vaccination in the preceding 1–3 months (Odds Ratio, 1.20 [95% confidence interval, 1.07–1.35]). This association was marked among women residing in the most deprived municipalities (1.28 [1.07–1.52]) and those who were not using hormonal contraception (1.28 [1.11–1.48]). Assuming a causal relationship, a total of 103 cases [54–196] were estimated to be attributable to primary vaccination in France.

Conclusion: These findings provide evidence of an increased risk of heavy menstrual bleeding during the three-month period following primary COVID-19 mRNA vaccination. No increased risk was found beyond 3 months after primary vaccination nor following booster doses.

1. Introduction

In October 2022, following reports of abnormal menstrual bleeding cases, the European Medicines Agency (EMA) considered heavy menstrual bleeding as a potential side effect of the two mRNA-based COVID-19 vaccines Comirnaty (Pfizer/BioNTech) and Spivevax (Moderna), and products information were updated accordingly [1]. Reported cases of heavy menstrual bleeding, mostly qualified as non-severe and self-resolving, occurred after the first, second and booster doses.

Several epidemiological studies have investigated the relationship between COVID-19 vaccination and menstrual disorders [2–12], but findings are inconsistent regarding the risk of heavy menstrual bleeding. In the Norwegian MoBa cohort, the risk of heavier and longer-than-usual bleeding was 60% higher in the first cycle after vaccination than in the

* Corresponding author at: Epi-Phare ANSM-CNAM, 143/147 Bd Anatole France, 93285 Saint-Denis Cedex, France.
E-mail address: jeremie.botton@ansm.sante.fr (J. Botton).

https://doi.org/10.1016/j.vaccine.2024.126252
Received 28 March 2024; Received in revised form 9 August 2024; Accepted 17 August 2024
Available online 2 September 2024

cycle preceding vaccination in girls aged 12–15 years [3], and nearly twice as high in the six weeks after the first or second dose in women aged 18–30 years [4]. A slightly increased risk of greater bleeding quantity was also found following the first COVID-19 vaccine dose in a US cohort study of women with normal menstrual cycles [5]. In contrast, in a large cohort study of pre-menopausal Swedish women, no increase in healthcare contacts for heavy menstrual bleeding was reported in the 8–90 days following vaccination [2], although in this study and in another one [13], COVID-19 vaccination was found associated with unexpected vaginal bleeding in women without menstruation. Furthermore, COVID-19 vaccination, unlike COVID-19 disease, was not associated with self-reported changes in menstruation bleeding quantity in a UK retrospective study [6]. Heterogeneity of the risk according to the way menstrual disorders were identified and the timing and dose of vaccination considered may explain such differences [7,11].

This study aimed to thoroughly assess the risk of heavy menstrual bleeding requiring hospital care following COVID-19 vaccination among women aged 15–50 years in France according to the number of doses received and the time elapsed since vaccination.

2. Methods

2.1. Data source

As in previous studies conducted by our group Epi-Phare [14–17], this study used individual data from four French national data sources: the Système National des Données de Santé (SNDS), the Système d'Information sur les Vaccins anti-COVID-19 (VAC-SI), the Système d'Information sur le Dépistage (SI-DEP), and hospitalization data from the Programme de Médicalisation des Systèmes d'Information (PMSI). These databases, matched thanks to a unique individual anonymous identifier [18], contain comprehensive information for almost the entire French population. The SNDS includes information on socio-demographic characteristics and reimbursements for drugs, imaging and laboratory tests delivered or performed outpatient; the VAC-SI database contains information on COVID-19 vaccinations (products and injection dates); the SI-DEP database contains information on the dates and results of SARS-CoV-2 tests (polymerase chain reaction (PCR), antigenic or serological tests); the PMSI includes information on hospital care, including dates of hospital stays, inpatient procedures and discharge diagnoses.

2.2. Study population

The COVID-19 vaccination campaign started in France on December 27, 2020, first in the elderly population with comorbidities or in healthcare professionals, and was extended to all adults on May 12, 2021.

In this case-control study, eligible cases were all women aged 15 to 50 years with a hospital discharge diagnosis of heavy menstrual bleeding in France identified from PMSI hospitalization data, with a date of hospital admission between May 12, 2021 (date on which vaccination was made available to the general population in France) and August 31, 2022. Heavy menstrual bleeding was defined as any ICD-10 diagnosis code N92.x as principal or related hospital discharge diagnosis: N92.0 “Excessive and frequent menstruation with regular cycle”, N92.1 “Excessive and frequent menstruation with irregular cycle”, N92.5 “Other specified irregular menstruation”, N92.6 “Irregular menstruation, unspecified”. In the French version of the ICD-10 [19], N92 code refers to “Menorrhagia, polymenorrhoea and metrorrhagia”, therefore N92.x codes generally correspond to cases with heavy menstrual bleeding.

Each case was matched to up to 30 randomly selected controls who did not have any hospital discharge diagnosis (principal, related or associated) of excessive, frequent or irregular menstruation (ICD-10 code: N92) or other abnormal uterine or vaginal bleeding (ICD-10 code: N93) during the study period. Matching criteria were year of birth, location of residence (*département*), level of social deprivation index of the municipality of residence [20] (low [social deprivation index in two most deprived quintiles of the distribution in France] or high [three least deprived quintiles]) and contraceptive method used in the last six months (hormonal contraceptive excluding intrauterine device [IUD] / hormonal IUD / non-hormonal IUD / other or no contraception). Cases' date of hospital admission was used as the index date for cases and their matched controls.

Eligible cases and controls with one of the following criteria were excluded: (i) women who at the index date had a history of pregnancy in the preceding 18 months, a history of hysterectomy or coagulation disorder in the preceding five years, or a history of antithrombotic drug use in the preceding 3 months; (ii) women vaccinated before 12 May 2021 - as in France vaccination was then restrained to specific categories of the population (*i.e.*, women at high risk of severe COVID-19, health professionals); (iii) women who had not used the healthcare system for the last 2 years prior to the index date (for whom healthcare identification in the SNDS could be an issue).

2.3. Exposure

Exposure was defined by the type of last COVID-19 vaccination received (primary vaccination [first or second dose] or booster [third or higher dose]) and the elapsed time since its administration ($\leq$1 month, 1 to 3 months, 3 to 6 months, 6 to 9 months and $>$ 9 months) at the index date. Women who had not received any COVID-19 vaccine by the index date were considered unexposed.

2.4. Covariates

In addition to characteristics used as matching variables, various covariates potentially associated with the risk of hospital care for heavy menstrual bleeding and with COVID-19 vaccination were considered. All these covariates were measured at the index date. Sociodemographic characteristics included affiliation to solidarity-based complementary health insurance (C2S, allowing free access to health care for people with low incomes) and size of the municipality of residence (below or above 50,000 inhabitants). Healthcare use indicators included the numbers of outpatient visits to a GP and to a specialist in gynaecology, and the number of hospital stays (excluding for obstetrical reasons) over the period 2018–2019, *i.e.* before the COVID-19-related disruptions in healthcare access (eTable 1). The following comorbidities, identified in the five years prior to the index date based on hospital discharge and long-term disease diagnoses, reimbursed treatments and medical procedures (eTables 2 and 3), were considered: obesity, smoking, and alcohol use disorders; diabetes, hypertension, cardiovascular disease, chronic respiratory disease, mental disorder, cancer, autoimmune disorder, anaemia, genital tract disorder (including leiomyoma, endometriosis, polyps, other non-inflammatory diseases and inflammatory disorders); and five years history of heavy menstrual bleeding. Recent SARS-CoV-2 infection was identified by a positive PCR or antigenic test or a hospitalization for COVID-19 in the preceding two months. Characteristics of cases' hospital stay included information on the length of stay, on admission to the emergency department or to an intensive care unit, and on any hospital discharge diagnosis of anaemia or blood transfusion during the stay. Information was also available on any death within the 30 days of hospital admission.

2.5. Statistical analysis

Conditional logistic regression models were used to estimate Odds Ratios (OR) of hospital care for heavy menstrual bleeding associated with exposure, adjusting for sociodemographic characteristics, healthcare use indicators, comorbidity and recent SARS-CoV-2 infection. Analyses were conducted overall and separately according to age (15–34 or 35–50 years), level of social deprivation index (low or high) and use of

hormonal contraception (yes or no). Because we are studying biological relationships rather than random numbers, and because real associations are to be expected [21], we did not adjust for multiple tests but rather interpreted the results cautiously and according to biological plausibility and to available knowledge.

Various sensitivity analyses were performed to assess the robustness of the results. First, the study population was restricted by excluding (a) women aged below 18 years, (b) C2S beneficiaries and (c) women with a history of SARS-CoV-2 infection in the two months before index date. Second, analyses were conducted using tighter identification criteria for heavy menstrual bleeding, *i.e.* (d) restriction to ICD-10 codes N92.0 or N92.1 only (*i.e.* the most specific ICD-10 codes of heavy menstrual bleeding), (e) exclusion of women with a history of heavy menstrual bleeding diagnosis in the preceding year, and (f) exclusion of women with an identified cause of heavy menstrual bleeding (including cancer, auto-immune or genital tract disorder) or a history of anaemia or heavy menstrual bleeding in the preceding five years.

To characterize the potential effect of an unmeasured confounding bias, we determined the e-value [22]. This represents the strength of the association that would have been necessary between this confounding factor and heavy menstruation on the one hand, and between this confounding factor and the vaccine on the other hand, to explain the observed association.

Using the odds ratio as an estimate of relative risk and assuming a causal relationship, we estimated the total number of cases attributable to the vaccine by multiplying the observed number of exposed cases by the ratio (OR - 1)/OR, and the attributable fraction by dividing the result by the total number of women aged 15 to 50 years vaccinated during the study period [23]. Confidence intervals were calculated by the delta method [17,24].

The analyses were performed using SAS 9.4 in SAS Enterprise Guide software, Version 7.15. Copyright © 2013 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

3. Results

3.1. Study population

A total of 7269 women aged 15 to 50 years with a hospital discharge diagnosis of heavy menstrual bleeding between May 12, 2021 and August 31, 2022 were matched to 193,443 women without any hospital diagnosis of abnormal gynaecologic bleeding over the same period (Fig. 1). After excluding pregnant or post-parturient women, those hysterectomized, with coagulation disorder or history of antithrombotic drug use, and those vaccinated before May 12, 2021, or not identifiable in the SNDS, 4610 cases and 89,375 controls were included. Each included case had 20 matched controls in median (IQR 17 to 23), and 92% had >10 controls (eFigure 1).

3.2. Characteristics of cases and controls

Cases' index date was distributed throughout the study period, with no clear temporal trend between May 2021 and August 2022 (eFigure 2). At the index date, cases and controls were aged 42 years in median, and >60% were aged between 40 and 50 years (Table 1). They lived all over France, mainly in municipalities with a low level of social deprivation (cases: 54.5%, controls: 53.6%). Approximately 30% were using hormonal contraception (cases: 33.2%, controls: 28.6%). Cases were more often than controls affiliated to the C2S (21.6% *versus* 16.5%). Their level of healthcare use was higher: in 2018–2019 they were more likely to have had more than five visits to a GP (60.9% *versus* 47.6%), to have visited a specialist in gynaecology at least once (57.1% *versus* 44.2%), and to have been hospitalized (30.8% *versus* 18.3%). Cases were also more often affected by certain comorbidities such as obesity, diabetes, cardiovascular diseases, mental disorders, cancer, autoimmune diseases, anaemia, and disorders of the genital tract (13.9% *versus* 3.8% - mainly leiomyomas, polyps and endometriosis, excluding identification at index date). Cases were more likely to have a history of heavy menstrual bleeding in the preceding 5 years (4.9% *versus* 0.6%) and they slightly more often had a history of SARS-CoV-2 infection in the preceding two months (6.5% *versus* 5.8%).

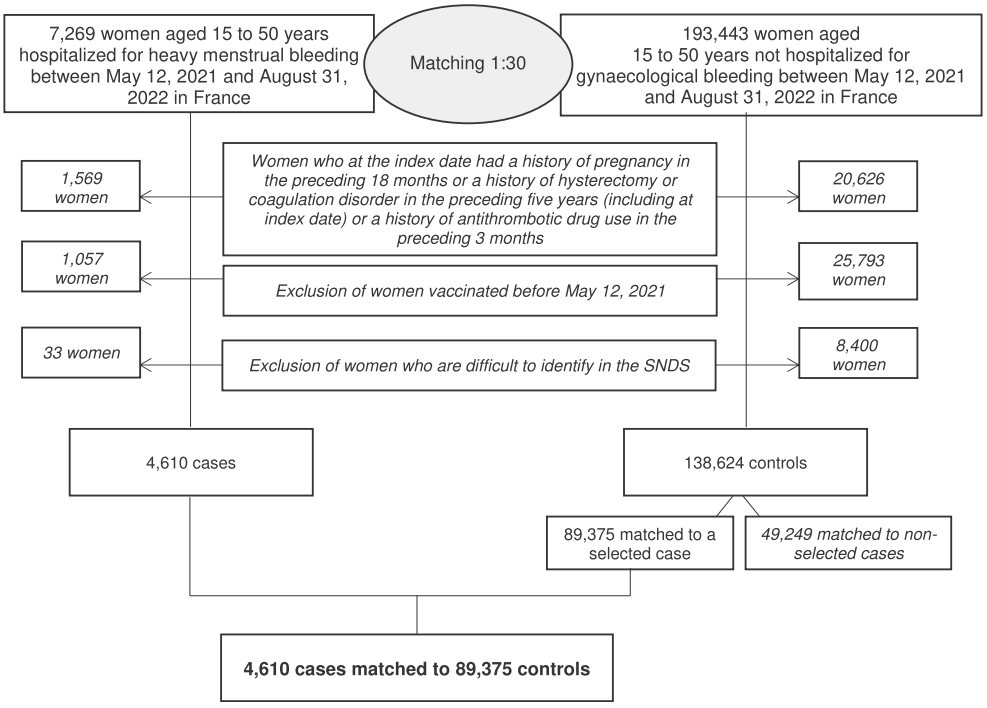


Figure 1. Flowchart

Table 1
Characteristics of cases and controls at index date.

	Controls	Cases
	$N = 89,375$	$N = 4610$
Sociodemographic characteristics*		
Age in years		
Mean (SD)	38.9 (9.5)	39.3 (9.0)
Median (IQR)	42 [34–46]	42 [35–46]
15–24 years	11,352 (12.7)	473 (10.2)
25–34 years	11,204 (12.5)	644 (14.0)
35–44 years	35,028 (39.2)	1840 (39.9)
45–50 years	31,791 (35.6)	1653 (35.9)
Solidarity-based complementary health insurance (C2S)	14,750 (16.5)	998 (21.6)
Region of residence		
Paris region	13,941 (15.6)	717 (15.6)
North-West	16,826 (18.8)	844 (18.3)
North-North-East	23,192 (25.9)	1206 (26.2)
South-East	19,074 (21.3)	1004 (21.8)
South-West	13,693 (15.3)	704 (15.3)
Overseas departments	2649 (3.0)	135 (2.9)
Size of the municipality of residence		
$\leq$ 50,000 inhabitants	70,246 (78,6)	3651 (79,2)
$>$ 50,000 inhabitants	19,122 (21.4)	958 (20.8)
Level of social deprivation of the municipality of residence		
Low	47,918 (53.6)	2511 (54.5)
High	41,457 (46.4)	2099 (45.5)
Contraception use*		
Hormonal contraceptive excluding intrauterine device	17,040 (19.1)	899 (19.5)
Hormonal intrauterine device (IUD)	8494 (9.5)	633 (13.7)
Non hormonal IUD	3097 (3.5)	268 (5.8)
None or other non-hormonal contraceptive	60,744 (68.0)	2810 (61.0)
Healthcare use indicators		
Number of outpatient visits to a GP in 2018–2019		
0	9906 (11.1)	369 (8.0)
1 to 2	15,005 (16.8)	538 (11.7)
3 to 5	21,887 (24.5)	894 (19.4)
6 to 10	22,967 (25.7)	1296 (28.1)
11 or higher	19,610 (21.9)	1513 (32.8)
Number of outpatient visits to a specialist in gynaecology in 2018–2019		
0	49,826 (55.8)	1980 (42.9)
1–2	25,347 (28.4)	1558 (33.8)
3 or higher	6054 (6.7)	606 (13.2)
Pregnancy during the period 2018–2019	8148 (9.1)	466 (10.1)
Number of hospital stays** in 2018–2019		
0	72,990 (81.7)	3189 (69.2)
1 to 2	14,532 (16.3)	1183 (25.7)
3 or higher	1853 (2.0)	238 (5.1)
Comorbidity		
Disorders related to		
Alcohol consumption	1028 (1.2)	58 (1.3)
Tobacco smoking	6018 (6.7)	374 (8.1)
Obesity	2571 (2.9)	282 (6.1)
Diabetes	1337 (1.5)	117 (2.5)
Hypertension	4214 (4.7)	332 (7.2)
Cardiovascular disease	750 (0.8)	63 (1.4)
Chronic respiratory disease	3137 (3.5)	208 (4.5)
Mental disorder	10,074 (11.3)	713 (15.5)
Cancer	1623 (1.8)	217 (4.7)
Auto-immune disorder	1711 (1.9)	115 (2.5)
Anaemia	1226 (1.4)	389 (8.4)
Genital tract disorder	3438 (3.8)	640 (13.9)
History of heavy menstrual bleeding in the preceding 5 years	493 (0.6)	224 (4.9)
Recent SARS-CoV-2 infection		
History of SARS-CoV-2 infection in the preceding 2 months	5167 (5.8)	298 (6.5)

Numbers are n (%) unless stated otherwise.
SD: Standard Deviation; IQR: Inter Quartile Range.
* In spite of matching, age, region, deprivation index and contraception use were slightly unbalanced due to heterogeneous numbers of controls by case (eFigure 1).
** Excluding hospital stays for obstetrical reasons.

Table 2
Association between hospital care for heavy menstrual bleeding and time since the last COVID-19 vaccine injection, overall and according to the type of last vaccination.

	Controls (N = 89,375)	Cases (N = 4610)	Crude OR [95% CI]	Adjusted* OR [95% CI]
Overall				
Unvaccinated	26,571 (29.7%)	1326 (28.8%)	1.0 [reference]	1.0 [reference]
Vaccinated *(62,804 controls / 3284 cases)*				
Last injection within ≤1 month	11,273 (12.6%)	539 (11.7%)	0.92 [0.83–1.03]	0.97 [0.86–1.09]
Last injection within 1–3 months	16,859 (18.9%)	940 (20.4%)	1.11 [1.00–1.22]	1.15 [1.04–1.28]
Last injection within 3–6 months	22,506 (25.2%)	1152 (25.0%)	0.99 [0.90–1.09]	1.02 [0.92–1.13]
Last injection within 6–9 months	8643 (9.7%)	472 (10.2%)	1.10 [0.96–1.25]	1.11 [0.97–1.27]
Last injection within >9 months	3523 (3.9%)	181 (3.9%)	1.06 [0.88–1.26]	1.05 [0.88–1.27]
According to the type of last vaccination				
Unvaccinated	26,571 (29.7%)	1326 (28.8%)	1.0 [reference]	1.0 [reference]
Vaccinated with a primary vaccination as last vaccination *(41,405 controls / 2219 cases)*				
Last injection within ≤1 month	8536 (9.6%)	415 (9.0%)	0.96 [0.85–1.08]	0.99 [0.87–1.12]
Last injection within 1–3 months	10,704 (12.0%)	617 (13.4%)	1.17 [1.04–1.31]	1.20 [1.07–1.35]
Last injection within 3–6 months	13,543 (15.2%)	715 (15.5%)	1.03 [0.92–1.15]	1.05 [0.93–1.18]
Last injection within 6–9 months	5099 (5.7%)	291 (6.3%)	1.12 [0.96–1.29]	1.10 [0.94–1.28]
Last injection within >9 months	3523 (3.9%)	181 (3.9%)	0.98 [0.82–1.18]	1.00 [0.83–1.21]
Vaccinated with a booster vaccination as last vaccination *(21,399 controls / 1065 cases)*				
Last injection within ≤1 month	2737 (3.1%)	124 (2.7%)	0.86 [0.70–1.06]	0.93 [0.75–1.16]
Last injection within 1–3 months	6155 (6.9%)	323 (7.0%)	1.02 [0.88–1.19]	1.07 [0.92–1.26]
Last injection within 3–6 months	8963 (10.0%)	437 (9.5%)	0.89 [0.78–1.03]	0.94 [0.81–1.09]
Last injection within 6–9 months	3544 (4.0%)	181 (3.9%)	0.94 [0.77–1.16]	1.05 [0.85–1.30]
Last injection within >9 months	0	0	–	–

OR: Odds-Ratio; CI: Confidence Interval.
* Conditional logistic regression adjusted for sociodemographic characteristics, healthcare use indicators, comorbidity and recent SARS-CoV-2 infection.

3.3. Characteristics of cases' hospital stay

Most cases (70.8% of unvaccinated cases and 78.3% of vaccinated cases) did not stay at hospital overnight (eTable 4), while 6.0% and 2.5%, respectively, spent three or more nights in hospital. Among the cases, 27.8% of the unvaccinated and 18.2% of the vaccinated women were admitted to the emergency department, and 0.7% and 0.2%, respectively, to an intensive care unit. Two women died within the 30 days following their hospital admission, one unvaccinated (a 42 years old woman with traumatic uterine injuries and septic shock) and one vaccinated (a 28 years old woman diagnosed with a colorectal cancer).

3.4. Association between COVID-19 vaccination and hospital care for heavy menstrual bleeding

At the index date, cases were slightly more frequently vaccinated against COVID-19 than controls (71.2% *versus* 70.3%), and among those vaccinated the last vaccine received was more frequently a dose of primary vaccination (67.6% *versus* 65.9%) and less frequently a booster dose (32.4% *versus* 34.1%) (eTable 5). For both cases and controls, the last vaccine received was almost exclusively an mRNA vaccine (Comirnaty: 75.9% and 74.9%; Spikevax: 23.8% and 24.8%, respectively), administered 104 days earlier in median for both. Cases had more frequently than controls received their last dose in the preceding 1 to 3 months (20.4% *versus* 18.9%) or 6 to 9 months (10.2% *versus* 9.7%).

In multivariable analysis, the risk of hospital care for heavy menstrual bleeding was higher in women who had received a last dose of vaccine (either primary vaccination or booster dose) in the preceding 1 to 3 months than in those unvaccinated (adjusted OR, 1.15 [95% CI, 1.04–1.28]), while the risk did not differ for women whose last vaccine dose was administered in the preceding month (OR, 0.97 [95% CI, 0.86–1.09] or beyond 3 months earlier (OR ranging from 1.02 to 1.11) (Table 2). Similar results were observed when considering women whose last dose received was a dose of primary vaccination, among whom the risk of hospital care for heavy menstrual bleeding was increased between 1 and 3 months after this vaccination (OR, 1.20 [95% CI, 1.07–1.35]), but not within one month (OR, 0.99 [95% CI, 0.87–1.12]) nor beyond 3 months after vaccination (OR ranging from 1.00 to 1.10). In contrast, the risk of hospital care for heavy menstrual bleeding after a booster dose did not differ from that of unvaccinated women, regardless of the time since last injection (OR ranging from 0.93 to 1.07).

The risk of heavy menstrual bleeding between 1 and 3 months after primary vaccination was similar in women aged 15 to 34 years (OR, 1.22 [95% CI, 0.96–1.55]) and those aged 35 to 50 years (OR, 1.20 [95% CI, 1.05–1.38]) (Table 3 and eTable 6). In contrast, while the association was marked among women residing in the most deprived municipalities (OR, 1.28 [95% CI, 1.07–1.52], eTable 7) and among those who were not using hormonal contraception (OR, 1.28 [95% CI, 1.11–1.48], eTable 8), no significant association was found in women residing in municipalities with a low deprivation index (OR, 1.15 [95% CI, 0.98–1.35]) and those using hormonal contraception (OR, 1.02 [95% CI, 0.82–1.27]).

Sensitivity analyses did not substantially alter the associations between hospital care for heavy menstrual bleeding and primary vaccination in the preceding 1 to 3 months (Table 4). The e-value was 1.69, with a lower bound of the 95% confidence interval at 1.34.

Assuming a causal relationship, the estimated number of cases attributable to primary vaccination in France between May 12, 2021 and August 31, 2022 was 103 [54–196], corresponding to a rate of 7.9 [4.1–15.0] cases per million vaccinated women among the total 13,054,285 women aged 15 to 50 years vaccinated overall.

4. Discussion

In this case-control study based on data from the whole population of women aged 15–50 years in France, we identified a moderately increased risk (+20%) of heavy menstrual bleeding requiring hospital care (mainly short, non-overnight hospital stays which did not require transfusion or intensive care) within 1 to 3 months after primary vaccination with a COVID-19 mRNA vaccine. It is estimated that this increased risk translated into approximately 100 excess cases at the scale of the 13 million women vaccinated in France between May 2021 and August 2022. In contrast, no increased risk was identified beyond 3 months after primary vaccination nor following booster vaccination.

Post-vaccination menstrual disorders have been reported with other

Table 3
Association between hospital care for heavy menstrual bleeding and time since last COVID-19 vaccination¶ by age, social deprivation index and use of hormonal contraception.*

¶ *For the sake of clarity, only results for primary vaccination as last COVID-19 vaccination are reported in this table. Complete results including those for booster vaccination as last COVID-19 vaccination are presented as supplementary material (eTables 6-8).*

	Controls	Cases	Crude OR [95% CI]	Adjusted* OR [95% CI]
By age				
15–34 years *(22,556 controls / 1117 cases)*				
Unvaccinated	7507 (33.3%)	374 (33.5%)	1.0 [reference]	1.0 [reference]
Vaccinated with a primary vaccination as last vaccination				
Last injection within ≤1 month	2031 (9.0%)	97 (8.7%)	0.99 [0.77–1.26]	1.07 [0.83–1.39]
Last injection within 1–3 months	2416 (10.7%)	139 (12.4%)	1.15 [0.92–1.45]	1.22 [0.96–1.55]
Last injection within 3–6 months	3391 (15.0%)	166 (14.9%)	0.94 [0.75–1.18]	0.97 [0.77–1.22]
Last injection within 6–9 months	1708 (7.6%)	95 (8.5%)	1.08 [0.83–1.41]	1.07 [0.81–1.42]
Last injection within >9 months	1148 (5.1%)	50 (4.5%)	0.84 [0.59–1.19]	0.87 [0.60–1.26]
35–50 years *(66,819 controls / 3493 cases)*				
Unvaccinated	19,064 (28.5%)	952 (27.3%)	1.0 [reference]	1.0 [reference]
Vaccinated with a primary vaccination as last vaccination				
Last injection within ≤1 month	6505 (9.7%)	318 (9.1%)	0.95 [0.82–1.09]	0.97 [0.84–1.12]
Last injection within 1–3 months	8288 (12.4%)	478 (13.7%)	1.18 [1.03–1.34]	1.20 [1.05–1.38]
Last injection within 3–6 months	10,152 (15.2%)	549 (15.7%)	1.06 [0.93–1.21]	1.08 [0.94–1.23]
Last injection within 6–9 months	3391 (5.1%)	196 (5.6%)	1.12 [0.94–1.34]	1.11 [0.92–1.34]
Last injection within >9 months	2375 (3.6%)	131 (3.8%)	1.04 [0.84–1.29]	1.06 [0.85–1.32]
By social deprivation index				
Low social deprivation index *(47,918 controls / 2511 cases)*				
Unvaccinated	13,247 (27.6%)	683 (27.2%)	1.0 [reference]	1.0 [reference]
Vaccinated with a primary vaccination as last vaccination				
Last injection within ≤1 month	4598 (9.6%)	223 (8.9%)	0.92 [0.77–1.08]	0.94 [0.79–1.12]
Last injection within 1–3 months	5859 (12.2%)	333 (13.3%)	1.10 [0.94–1.29]	1.15 [0.98–1.35]
Last injection within 3–6 months	7488 (15.6%)	407 (16.2%)	1.03 [0.89–1.20]	1.07 [0.91–1.25]
Last injection within 6–9 months	2957 (6.2%)	186 (7.4%)	1.21 [1.00–1.47]	1.24 [1.02–1.51]
Last injection within >9 months	2046 (4.3%)	101 (4.0%)	0.92 [0.72–1.18]	0.94 [0.73–1.21]
High social deprivation index *(41,457 controls / 2099 cases)*				
Unvaccinated	13,324 (32.1%)	643 (30.6%)	1.0 [reference]	1.0 [reference]
Vaccinated with a primary vaccination as last vaccination				
Last injection within ≤1 month	3938 (9.5%)	192 (9.1%)	1.01 [0.84–1.21]	1.05 [0.87–1.26]
Last injection within 1–3 months	4845 (11.7%)	284 (13.5%)	1.25 [1.06–1.48]	1.28 [1.07–1.52]
Last injection within 3–6 months	6055 (14.6%)	308 (14.7%)	1.03 [0.87–1.22]	1.03 [0.86–1.23]
Last injection within 6–9 months	2142 (5.2%)	105 (5.0%)	0.97 [0.77–1.23]	0.93 [0.73–1.18]
Last injection within >9 months	1477 (3.6%)	80 (3.8%)	1.06 [0.81–1.39]	1.09 [0.82–1.44]

	Controls	Cases	Crude OR [95% CI]	Adjusted* OR [95% CI]
By hormonal contraception use				
No hormonal contraception *(63,841 controls / 3078 cases)*				
Unvaccinated	20,626 (32.3%)	923 (30.0%)	1.0 [reference]	1.0 [reference]
Vaccinated with a primary vaccination as last vaccination				
Last injection within ≤1 month	5760 (9.0%)	276 (9.0%)	1.07 [0.92–1.24]	1.05 [0.90–1.22]
Last injection within 1–3 months	7356 (11.5%)	410 (13.3%)	1.30 [1.13–1.49]	1.28 [1.11–1.48]
Last injection within 3–6 months	9252 (14.5%)	467 (15.2%)	1.15 [1.00–1.32]	1.11 [0.96–1.28]
Last injection within 6–9 months	3683 (5.8%)	202 (6.6%)	1.23 [1.03–1.46]	1.17 [0.98–1.40]
Last injection within >9 months	2632 (4.1%)	124 (4.0%)	1.05 [0.84–1.31]	1.02 [0.81–1.28]
Hormonal contraception *(25,534 controls / 1532 cases)*				
Unvaccinated	5945 (23.3%)	403 (26.3%)	1.0 [reference]	1.0 [reference]
Vaccinated with a primary vaccination as last vaccination				
Last injection within ≤1 month	2776 (10.9%)	139 (9.1%)	0.75 [0.60–0.93]	0.87 [0.70–1.10]
Last injection within 1–3 months	3348 (13.1%)	207 (13.5%)	0.90 [0.73–1.11]	1.02 [0.82–1.27]
Last injection within 3–6 months	4291 (16.8%)	248 (16.2%)	0.78 [0.64–0.96]	0.90 [0.72–1.12]
Last injection within 6–9 months	1416 (5.5%)	89 (5.8%)	0.85 [0.65–1.11]	0.93 [0.69–1.25]
Last injection within >9 months	891 (3.5%)	57 (3.7%)	0.80 [0.57–1.12]	0.94 [0.66–1.34]

OR: Odds-Ratio; CI: Confidence Interval.
* Conditional logistic regression adjusted for sociodemographic characteristics, healthcare use indicators, comorbidity and recent SARS-CoV-2 infection.

vaccinations [25–27]. While the mechanism is not fully understood, different hypotheses involving the hypothalamic-pituitary-ovarian axis have been proposed [28,29]. Besides, immune changes are known to be implicated in some menstrual disturbances including heavy menstrual bleeding [30]. Immune-mediated vaccine-induced thrombocytopenia has also been proposed as a hypothesis [31], although thrombocytopenia was less frequently reported for mRNA-based compared to adenoviral-based vaccines [32].

Our findings are consistent with most of previous published studies suggesting a relatively modest association between COVID-19 vaccination and heavy menstrual bleeding, with a spontaneously reversible effect [3–5,9,13]. However, two large studies did not find any association between COVID-19 vaccination and heavy menstrual bleeding [2,6]. The discrepancy between our findings and those of these two studies may result from methodological differences. In the Swedish study by Ljung *et al* [2], which did not provide evidence for increased healthcare

Table 4
Association between hospital care for heavy menstrual bleeding and primary vaccination as last vaccination in the preceding 1–3 months: Sensitivity analyses.

	Controls	Cases	Crude OR [95% CI]	Adjusted* OR [95% CI]
Restriction of the study population				
Exclusion of women aged 15–17 years *(86,207 controls / 4484 cases)*				
Unvaccinated	25,362 (29.4%)	1275 (28.4%)	1.0 [reference]	1.0 [reference]
Primary vaccination as last vaccination within 1–3 months	10,356 (12.0%)	600 (13.4%)	1.17 [1.04–1.31]	1.20 [1.07–1.36]
Exclusion of C2S beneficiaries *(59,123 controls / 3611 cases)*				
Unvaccinated	15,375 (26.0%)	911 (25.2%)	1.0 [reference]	1.0 [reference]
Primary vaccination as last vaccination within 1–3 months	7575 (12.8%)	515 (14.3%)	1.19 [1.04–1.36]	1.18 [1.03–1.35]
Exclusion of women with history of SARS-CoV-2 infection in the 2 months before index date *(79,390 controls / 4312 cases)*				
Unvaccinated	24,242 (30.5%)	1247 (28.9%)	1.0 [reference]	1.0 [reference]
Primary vaccination as last vaccination within 1–3 months	10,037 (12.6%)	601 (13.9%)	1.19 [1.06–1.34]	1.22 [1.08–1.38]
Restriction of cases' definition criteria				
Restriction to the most specific ICD-10 codes of heavy menstrual bleeding *(75,896 controls / 3921 cases)*				
Unvaccinated	22,381 (29.5%)	1137 (29.0%)	1.0 [reference]	1.0 [reference]
Primary vaccination as last vaccination within 1–3 months	9129 (12.0%)	534 (13.6%)	1.17 [1.03–1.32]	1.19 [1.05–1.35]
Exclusion of cases with a history of heavy menstrual bleeding diagnosis in the preceding year *(88,576 controls / 4571 cases)*				
Unvaccinated	26,301 (29.7%)	1308 (28.6%)	1.0 [reference]	1.0 [reference]
Primary vaccination as last vaccination within 1–3 months	10,608 (12.0%)	614 (13.4%)	1.18 [1.05–1.32]	1.21 [1.07–1.36]
Exclusion of cases with an identified cause of heavy menstrual bleeding *(55,372 controls / 3067 cases)*				
Unvaccinated	16,497 (29.8%)	870 (28.4%)	1.0 [reference]	1.0 [reference]
Primary vaccination as last vaccination within 1–3 months	6478 (11.7%)	407 (13.3%)	1.21 [1.05–1.40]	1.24 [1.07–1.42]

OR: Odds-Ratio; CI: Confidence Interval.
* Conditional logistic regression adjusted for sociodemographic characteristics, healthcare use indicators, comorbidity and recent SARS-Cov-2 infection.

contacts for menstrual bleeding disorders after vaccination based on Swedish general population registers, the risk period considered began very early (as early as 8 days) after vaccination, which may have masked a possible increase in risk occurring somewhat later. In contrast, in our study the risk was increased in the second and third months after vaccination, but not in the first month, probably reflecting the delay between the onset of symptoms and their management in hospital. Furthermore, >99% of menstrual bleeding disorders in the Swedish study were from specialist outpatient care, for which the information available did not make it possible to distinguish between visits motivated by a disorder appeared after COVID-19 vaccination and those scheduled for a longer time for an older problem, which may have led to underestimate a potential increase in risk. In our study, only cases requiring hospitalization were considered. Since time to care is probably shorter for these severe cases than for outpatients, the risk underestimation may be less acute. In the study by Alvergne *et al* [6], the delay since COVID-19 vaccination was not accounted for, and menstrual bleeding disorders were self-reported, which may have led to misclassification.

The validity of cases identified based on hospital diagnoses is supported by our finding of an increased risk limited to women not using hormonal contraception, *i.e.* those with spontaneous menstrual periods rather than withdrawal bleeding, as well as the robustness of the results to variations in case definition. However, considering only cases identified at hospital also has important consequences for the interpretation of the results. First, this implies that while the most severe cases were included, those for which an early outpatient management allowed avoiding hospitalization were not accounted for, suggesting that the overall frequency of heavy menstrual bleeding after COVID-19 vaccination is likely to be underestimated. In addition, restriction to cases identified at hospital may at least partly explain the absence of association observed among women residing in the least socioeconomically disadvantaged areas, among whom any problems of heavy menstrual bleeding may more likely be managed on an outpatient basis without the need for hospitalization.

This nationwide study benefited from the quality and comprehensiveness of the French National Health Data System. This allowed considering all cases of heavy menstrual bleeding managed at hospital which occurred throughout France during the 15-month period between May 2021 and August 2022, *i.e.* when most people got vaccinated against COVID-19. Furthermore, the completeness of the information available regarding COVID-19 vaccination allowed an accurate identification of the type of vaccination (*i.e.*, primary vaccination or booster dose) and of its timing, both for cases and controls.

Despite these strengths, it should be noted that the magnitude of the association between COVID-19 vaccination and heavy menstrual bleeding estimated in this study should be interpreted with caution. First, identifying diagnosis of heavy menstrual bleeding based on ICD-10 codes may have led to potential misclassification, and besides, we could not ensure that women included as controls were free of heavy menstrual bleeding if they were managed exclusively as outpatients; both issues may have led to a reduction in the contrast between cases and controls, resulting in a potential underestimation of the association. Furthermore, residual confounding cannot be definitely excluded, although we limited this risk by using adapted study design and statistical methods. Indeed, case-control matching and multivariable modelling allowed accounting for differences in measurable individual determinants of healthcare access and health status including age, socioeconomic characteristics and comorbidities. In addition, sensitivity analyses attested of the robustness of the results when excluding the youngest women, those most socially disadvantaged or with a recent history of SARS-CoV-2 infection. Nevertheless, since the estimated lower bound of the e-value confidence interval was close to 1, it cannot be fully excluded that unmeasured confounding explains the reported association between COVID-19 vaccination and heavy menstrual bleeding.

In conclusion, this study provides further support for the existence of an increased risk of heavy menstrual bleeding disorders following COVID-19 vaccination with mRNA vaccines. More specifically, it suggests that such an increased risk could occur during the three-month period following primary vaccination. Meanwhile, the results show no increase in the risk of heavy menstrual bleeding following booster doses.

Funding

This research did not receive any specific grant.

Credit authorship contribution statement

Jérémie Botton: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Marion Bertrand:** Writing – review &

editing, Methodology, Formal analysis, Data curation. **Marie-Joëlle Jabagi:** Writing – review & editing, Methodology, Conceptualization. **Lise Duranteau:** Writing – review & editing, Validation, Supervision, Methodology. **Kim Bouillon:** Writing – review & editing, Validation, Conceptualization. **Jérôme Drouin:** Writing – review & editing, Software, Data curation. **Laura Semenzato:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Stéphane Le Vu:** Writing – review & editing, Methodology. **Alain Weill:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Mahmoud Zureik:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Rosemary Dray-Spira:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of interest statement. None.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126252.

References

[1] EMA's safety committee. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 24–27 October 2022. European Medicines Agency. Published. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022; 2022.

[2] Ljung R, Xu Y, Sundström A, et al. Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study. BMJ 2023:e074778. https://doi.org/10.1136/bmj-2023-074778.

[3] Caspersen IH, Juvet LK, Feiring B, et al. Menstrual disturbances in 12- to 15-year-old girls after one dose of COVID-19 Comirnaty vaccine: population-based cohort study in Norway. Vaccine 2023;41(2):614–20. https://doi.org/10.1016/j.vaccine.2022.11.068.

[4] Trogstad L, Laake I, Robertson AH, et al. Heavy bleeding and other menstrual disturbances in young women after COVID-19 vaccination. Vaccine 2023;41(36):5271–82. https://doi.org/10.1016/j.vaccine.2023.06.088.

[5] Darney BG, Boniface ER, Van Lamsweerde A, et al. Impact of coronavirus disease 2019 (COVID-19) vaccination on menstrual bleeding quantity: an observational cohort study. BJOG An Int J Obstet Gynaecol 2023;130(7):803–12. https://doi.org/10.1111/1471-0528.17471.

[6] Alvergne A, Kountourides G, Argentieri MA, et al. A retrospective case-control study on menstrual cycle changes following COVID-19 vaccination and disease. iSci 2023;26(4):106401. https://doi.org/10.1016/j.isci.2023.106401.

[7] Maybin JA, Watters M, Rowley B, Walker CA, Sharp GC, Alvergne A. COVID-19 and abnormal uterine bleeding: potential associations and mechanisms. Clin Sci 2024;138(4):153–71. https://doi.org/10.1042/CS20220280.

[8] Brooks N, Irving SA, Kauffman TL, et al. Abnormal uterine bleeding diagnoses and care following COVID-19 vaccination. Am J Obstet Gynecol 2024;230(5):540.e1–540.e13. https://doi.org/10.1016/j.ajog.2024.01.006.

[9] Santangelo OE, Provenzano S, Grigis D, Ferrara C, Cedrone F, Firenze A. Menstrual changes after COVID-19 vaccine administration: a systematic review. Eur Rev Med Pharmacol Sci 2023;27(24):11664–71. https://doi.org/10.26355/eurrev_202312_34604.

[10] Duijster JW, Schoep ME, Nieboer TE, Jajou R, Kant A, van Hunsel F. Menstrual abnormalities after COVID-19 vaccination in the Netherlands: a description of spontaneous and longitudinal patient-reported data. Br J Clin Pharmacol 2023;89(10):3126–38. https://doi.org/10.1111/bcp.15799.

[11] Smaardijk VR, Jajou R, Kant A, van Hunsel FPAM. Menstrual disorders following COVID-19 vaccination: a review using a systematic search. Front Drug Saf Regul 2024;4(January):1–10. https://doi.org/10.3389/fdsfr.2024.1338466.

[12] Issakov G, Tzur Y, Friedman T, Tzur T. Abnormal uterine bleeding among COVID-19 vaccinated and recovered women: a National Survey. Reprod Sci 2023;30:713–21. https://doi.org/10.1007/s43032-022-01062-2.

[13] Blix K, Laake I, Juvet L, et al. Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. Sci Adv 2023;9(38):eadg1391. https://doi.org/10.1126/SCIADV.ADG1391/SUPPL_FILE/SCIADV.ADG1391_SM.PDF.

[14] Semenzato L, Botton J, Drouin J, et al. Characteristics associated with the residual risk of severe COVID-19 after a complete vaccination schedule: a cohort study of 28 million people in France. Lancet Reg Heal - Eur 2022;19:100441. https://doi.org/10.1016/j.lanepe.2022.100441.

[15] Botton J, Jabagi MJ, Bertrand M, et al. Risk for myocardial infarction, stroke, and pulmonary embolism following COVID-19 vaccines in adults younger than 75 years in France. Ann Intern Med 2022;175(9):1250–7. https://doi.org/10.7326/M22-0988.

[16] Jabagi M-J, Bertrand M, Botton J, et al. Stroke, myocardial infarction, and pulmonary embolism after bivalent booster. N Engl J Med Published online March 29, 2023. https://doi.org/10.1056/NEJMc2302134.

[17] Le Vu S, Bertrand M, Jabagi MJ, et al. Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines. Nat Commun 2022;13(1). https://doi.org/10.1038/S41467-022-31401-5.

[18] Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique 2017;65(Suppl. 4):S149–67. https://doi.org/10.1016/J.RESPE.2017.05.004.

[19] Organisation Mondiale de la Santé (OMS). *Classification Statistique Internationale Des Maladies et Des Problèmes de Santé Connexes - 10e Révision, Édition 2008*. 2008th ed. (WHO, ed.).; 2009. Accessed August 8, 2024, https://icd.who.int/browse10/Content/statichtml/ICD10Volume2_fr_2008.pdf.

[20] Rey G, Jougla E, Fouillet A, Hémon D. Ecological association between a deprivation index and mortality in France over the period 1997–2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Public Health 2009;9(1):33. https://doi.org/10.1186/1471-2458-9-33.

[21] Rothman KJ. Six persistent research misconceptions. J Gen Intern Med 2014;29(7):1060–4. https://doi.org/10.1007/s11606-013-2755-z.

[22] Haneuse S, Vanderweele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. Published online 2019. https://doi.org/10.1001/jama.2018.21554.

[23] Coughlin SS, Benichou J, Weed DL. Attributable risk estimation in case-control studies. Epidemiol Rev 1994;16(1):51–64. https://doi.org/10.1093/oxfordjournals.epirev.a036144.

[24] Greenland S. Variance estimators for attributable fraction estimates consistent in both large strata and sparse data. Stat Med 1987;6(6):701–8. https://doi.org/10.1002/sim.4780060607.

[25] Suzuki S, Hosono A. No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: results of the Nagoya study. Papillomavirus Res 2018;5:96–103. https://doi.org/10.1016/j.pvr.2018.02.002.

[26] Gong L, Ji H, huan, Tang X wen, Pan L yun, Chen X, Jia Y tao.. Human papillomavirus vaccine-associated premature ovarian insufficiency and related adverse events: data mining of vaccine adverse event reporting system. Sci Rep 2020;10(1):1–8. https://doi.org/10.1038/s41598-020-67668-1.

[27] Shingu T, Uchida T, Nishi M, et al. Menstrual abnormalities after hepatitis B vaccine. Kurume Med J 1983;29(3):123–5. https://doi.org/10.2739/KURUMEMEDJ.29.123.

[28] Nazir M, Asghar S, Rathore MA, et al. Menstrual abnormalities after COVID-19 vaccines: a systematic review. Vacunas 2022;23:S77–87. https://doi.org/10.1016/J.VACUN.2022.07.001.

[29] Alsalman M, Alhubail F, Bin Obaid F, et al. Impact of COVID-19 Vaccinations on Menstrual Bleeding. *Cureus*. Published online October 20. 2023. https://doi.org/10.7759/cureus.47360.

[30] Berbic M, Fraser IS. Immunology of normal and abnormal menstruation. Women Health 2013;9(4):387–95. https://doi.org/10.2217/WHE.13.32.

[31] Perricone C, Ceccarelli F, Nesher G, et al. Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases. Immunol Res 2014;60(2–3):226–35. https://doi.org/10.1007/s12026-014-8597-x.

[32] Kanack AJ, Padmanabhan A. Vaccine-induced immune thrombotic thrombocytopenia. Best Pract Res Clin Haematol 2022;35(3):101381. https://doi.org/10.1016/j.beha.2022.101381.