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ORIGINAL ARTICLE

Menstrual abnormalities after COVID-19 vaccination in the Netherlands: A description of spontaneous and longitudinal patient-reported data

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Aims: During the COVID-19 vaccination campaigns, the number of reports of menstrual abnormalities increased rapidly. Here, we describe the nature and potential risk factors associated with menstrual abnormalities based on spontaneously reporting data as well as data from a prospective cohort event monitoring (CEM) study as these are poorly studied.

Methods: Reports of menstrual abnormalities received by the Netherlands Pharmacovigilance Centre Lareb in the spontaneous reporting system between February 2021 and April 2022 were summarized. In addition, logistic regression analysis was performed on the reported menstrual abnormalities in the CEM study to assess the association between person characteristics, prior SARS-CoV-2 infection and use of hormonal contraceptives and the occurrence of menstrual abnormalities after vaccination.

Results: We analysed over 24 000 spontaneous reports of menstrual abnormalities and over 500 episodes (among 16 929 included women) of menstrual abnormalities in the CEM study. The CEM study showed an incidence of 41.4 per 1000 women aged ≤54 years. Amenorrhoea/oligomenorrhoea and heavy menstrual bleeding collectively accounted for about half of all abnormalities reported. Significant associations were observed for the age group 25–34 years (odds ratio 2.18; 95% confidence interval 1.45–3.41) and the Pfizer vaccine (odds ratio 3.04; 95% confidence interval 2.36–3.93). No association was observed for body mass index and presence of most comorbidities assessed.

Conclusion: The cohort study showed a high incidence of menstrual disorders among women aged ≤54 years, and this observation was supported by the analysis of

Abbreviations: AEFI, adverse event following immunization; CEM, cohort event monitoring; CIOMS, Council for International Organizations of Medical Sciences; IQR, interquartile range; TTO, time to onset; TTR, time to resolve.

Florence van Hunsel is the principal investigator of this study.

spontaneous reports. This suggests that a relation between COVID-19 vaccination and menstrual abnormalities is plausible and should be further investigated.

KEYWORDS

COVID-19, heavy menstrual bleeding, longitudinal cohort study, menstrual abnormalities, spontaneous reporting, vaccination

1 | INTRODUCTION

Since the onset of the vaccination programmes against SARS-CoV-2 infection, there has been substantial emphasis on the safety of the different vaccines being used, partially owing to the rapid development and implementation of the vaccines across the entire population in many countries. Based on the results of large-scale clinical trials, a selection of common adverse effects such as injection site reactions, fatigue and headache were included on the product information of COVID-19 vaccines.[1] In addition, previously unknown adverse events following immunization (AEFIs) have been recognized by regulatory authorities as related to the vaccines since the vaccinations campaigns started by the end of 2020. Examples hereof are thrombosis and thrombocytopenia syndrome for the viral vector vaccines from manufacturers AstraZeneca and Johnson & Johnson[2,3] and peri- and myocarditis for the mRNA vaccines from manufacturers BioNTech/Pfizer and Moderna[4] and the subunit protein vaccine from Novavax.[5]

Besides the official reports of adverse effects potentially associated with COVID-19 vaccination issued by international regulatory and public health authorities, such as the US Food and Drug Administration and the European Medicines Agency (EMA), concerns about a variety of different adverse health outcomes possibly related to vaccination were widely shared on (social) media channels.[6,7] Anecdotal reports of COVID-19 vaccines altering women's' menstrual cycle have been circulating on the Internet since the beginning of 2021.[8] Abnormalities in the menstrual cycle can include alterations in the menstrual cycle length, abnormal amount of menstrual blood loss, abnormal (pre) menstrual pain (dysmenorrhoea), intermenstrual bleeding or abnormal withdrawal bleeding. Some of these menstrual abnormalities can significantly diminish women's quality of life from several perspectives, such as by causing physical complaints (pain, tiredness), mental problems, work/school absenteeism. and reduced sports activities and sexual functioning.[9–11] Literature about background incidence of menstrual abnormalities is scarce and mostly addresses only menstrual abnormalities in adolescents or specific subpopulations.[12–14] Irregularities in the menstrual cycle and menses decline during adolescence as a result of maturation of the hypothalamic–pituitary–gonadal axis.[15] Nevertheless, menstrual abnormalities (mainly amenorrhoea, dysmenorrhoea and heavy menstrual bleeding) still occur in 20 to >50% of adolescent girls,[12,15,16] while heavy menstrual bleeding has been observed in 27–54% of adult women from several European countries.[9,14] A study from Iran showed a statistical higher prevalence of menstrual abnormalities in women aged <20 and ≥40 years.[17] Although the association between COVID-19 vaccines and menstrual abnormalities remained elusive for a relatively long period, the EMA recommended heavy menstrual bleeding to be added to the list of side effects on the product information of the mRNA vaccines of Moderna and Pfizer in October 2022.[18] However, the suggested association between vaccination and amenorrhoea/oligomenorrhoea was not sufficiently confirmative to be listed on the product information.[19]

In the Netherlands, the spontaneous reporting system for drugs and vaccines is maintained by the Netherlands Pharmacovigilance Centre Lareb. Continuous monitoring of vaccines/medicines is of critical importance for early detection of possible adverse effects in users as well as to mitigate (unwarranted) concerns in society by providing information about the incidence of adverse effects. In the period covered by the data in this study, 4 of the COVID-19 vaccines authorized by the EMA are being used in the Netherlands: Comirnaty (BioNTech/Pfizer), Vaxzevria (AstraZeneca), Spikevax (Moderna) and Jcovden (Johnson & Johnson), hereafter referred to as Pfizer, AstraZeneca, Moderna and Johnson & Johnson vaccine, respectively. Monitoring of COVID-19 vaccine safety is achieved through evaluation of spontaneous case reports of adverse events submitted by consumers and physicians. In addition, a prospective cohort event monitoring (CEM) study has been implemented in 2021 in which people were invited to record the occurrence of adverse events in a series of 6 questionnaires in the half year following their first COVID-19 vaccination.[20]

What is already known about this subject

- Many reports on menstrual abnormalities following COVID-19 vaccination have been issued worldwide.
- The European Medicines Agency recommended heavy menstrual bleeding to be added to the product information of the COVID-19 vaccines of Moderna and Pfizer as an adverse reaction with unknown frequency.

What this study adds

- Amenorrhoea/oligomenorrhoea and heavy menstrual bleeding collectively account for about half of all menstrual abnormalities reported.
- We found that the use of hormonal contraceptives was not consistently associated with the occurrence of menstrual abnormalities.

Lareb issued 2 reports, summarizing the received data on menstrual disorders, to the Dutch Medicines Evaluation Board in 2021 and 2022.[21,22] Currently, several studies have been published addressing the possible association between COVID-19 vaccination and menstrual abnormalities.[23–25] The majority of these studies had a cross-sectional design, in which outcomes varied widely from no observed association between menstrual abnormalities and COVID-19 vaccination to >60% of female participants who suffered from a specific menstrual abnormality.[26] A causal link between COVID-19 vaccination and menstrual abnormalities is to be further unravelled as are the possible risk factors thereof. Hence, in this study, we summarize the nature and characteristics of menstrual abnormalities reported to Lareb in the spontaneous reporting system and in data from the CEM study. In addition, we investigated factors possibly related to the occurrence or reporting of menstrual abnormalities in the CEM study. Moreover, we describe in more detail the information retrieved from the case reports of the 2 most reported menstrual abnormalities, amenorrhoea and heavy menstrual bleeding, to assess possible risk factors.

2 | METHODS

2.1 | Spontaneous reporting system

In the spontaneous reporting system, consumers and healthcare workers can send in an individual case report by completing a specific COVID-19 vaccine web-based reporting form. In the form, information is collected about the vaccine (brand, batch number, dose, date of the vaccination), the AEFI (type, latency, severity, treatment, duration) and personal/demographic information (age, weight, length, comorbidities, previous SARS-CoV-2 infection, concomitant use of medication).[27] People are also requested to consent the use of their e-mail address for additional follow-up questions by Lareb assessors if necessary. We calculated reporting rates of menstrual abnormalities per 100 000 administered vaccine doses, by age group, dose and vaccine brand. To this end, we retrieved the number of administered vaccines from the COVID-19 Vaccination Information and Monitoring System (CIMS), which is maintained by the RIVM National Institute for Public Health and the Environment.[28] Case reports of heavy menstrual bleeding and amenorrhoea were described in more detail as these were the most reported menstrual abnormalities in the spontaneous reporting system.

2.2 | CEM system

Inclusion for the CEM study occurred by means of flyers that were distributed among the vaccinees at a random selection of the vaccination locations in the Netherlands. For feasibility reasons, flyers were not distributed at all vaccination locations. Dutch residents aged ≥16 years and receiving their first COVID-19 vaccination between February and August 2021 were eligible to participate. Upon informed consent, participation included the completion of a baseline questionnaire upon registration (not later than 2 days after receiving the first dose of vaccination) and 6 follow-up questionnaires over a period of 6 months. Data collection occurred through web-based questionnaires using the Lareb Intensive Monitoring (LIM) system. In the baseline questionnaire, information was retrieved about age, sex, body weight and height, the preventive use of antipyretic drugs shortly before/after vaccination, history of polymerase chain reaction-confirmed SARS-CoV-2 infection before vaccination, presence of comorbidities and the concomitant use of medication. In the 6 follow-up questionnaires, participants could record the occurrence of any AEFI along with the time to onset (TTO), time to resolve (TTR) and the perceived burden of the AEFI (in 5 ordinal categories: not at all, slightly, somewhat, moderately, extremely). Participants in the CEM study received 1 or 2 doses of the AstraZeneca, Johnson & Johnson, Moderna or Pfizer vaccine. More details about the CEM study can be retrieved from Kant et al.[20] and Rolfes et al.[29]

2.3 | Categorization of variables

Both in the spontaneous reporting system and the CEM study, the reported AEFIs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology 23.0 and 24.0.[30] After consultation with gynaecologists, the reported menstrual abnormalities were categorized into 8 types of menstrual abnormalities, including amenorrhoea/oligomenorrhoea, dysmenorrhoea, heavy menstrual bleeding, intermenstrual blood loss, irregular blood loss, less menstrual blood loss, abnormal withdrawal blood loss and other. Table S1 displays the Preferred Term (PT) level MedDRA terms in each of the 8 categories. Age was categorized into 6 groups: <25, 25–34, 35–44, 45–54, 55–64 and ≥65 years. To assess the association between use of hormonal contraceptives and menstrual abnormalities in the CEM study, we classified the codes 'G02BA' and 'G02BB' from the Anatomical Therapeutic Chemical Classification System as 'topical use hormonal contraceptives' (including intrauterine and intravaginal contraceptives) and the Anatomical Therapeutic Chemical codes 'G03AA', 'G03AB', 'G03AC' and 'G03AD' as 'hormonal contraceptives'.[31] The criteria of the Council for International Organizations of Medical Sciences (CIOMS) were used to distinguish between serious and nonserious case reports: AEFIs that were life-threatening or that resulted in hospitalization, persistent or significant disability, congenital abnormalities, or death are considered serious.[32]

2.4 | Statistical analysis

To investigate possible associations between demographic, vaccine-related or health-related factors and the occurrence of menstrual abnormalities, logistic regression was applied to the data from the CEM study. We restricted the regression analyses to women aged ≤54 years as the nature of the few menstrual abnormalities reported by the oldest age group (>55 years) is doubtful, could be influenced

by a (post)menopausal state and might hamper the interpretation of the results. A series of univariable logistic regression was performed to identify factors associated with the occurrence of 'any menstrual abnormality' (i.e. regardless of the type of abnormality). Age group, vaccine brand, body mass index (BMI, in kg/m^2) and the presence of 13 different classes of comorbidities were assessed as predictor variables in univariable regression. The 13 classes of comorbidities included 'any comorbidity', allergy, cardiovascular disorder, diabetes, hepatic disease, hypertension, malignant tumour, neurological disorder, psychological disorder, renal disease, respiratory disease, suppressed immune function and 'other comorbidity'. Variables that were statistically significant in the univariable analysis were included in the multivariable analysis. Given that for most menstrual abnormalities, the numbers were too low to perform multivariable logistic regression on the separate types of abnormalities, we only analysed the abnormalities collectively. In a subanalysis, we also assessed the effect of hormonal contraceptive use on the occurrence of 'any menstrual abnormality' in a logistic regression model while adjusting for age. All analyses were performed using R-studio (version 1.3.1093). *P*-values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Spontaneous case reports

From 1 February 1 2021 to 29 March 2022, the Netherlands Pharmacovigilance Centre Lareb received a total of 24 090 case reports containing at least 1 menstrual disorder PT associated with a COVID-19 vaccine (Figure S1). Most women who reported a menstrual abnormality, received the Pfizer vaccine (79.0%, $n = 19\,076$), followed by Moderna (11.3%, $n = 2727$), Johnson & Johnson (6.8%, $n = 1647$) and AstraZeneca (2.6%, $n = 614$; Table 1). Overall, 19.3% of the women indicated a history of SARS-CoV-2 infection prior to vaccination in their case report. For all vaccines, except Johnson & Johnson (which was a single dose vaccine) and unknown vaccines, more case reports were received on the second vaccine dose compared to the first vaccine dose, although these differences were limited. The vast majority of case reports were sent in by consumers (99.5%, $n = 23\,958$), while the remaining 132 (0.5%) case reports were sent in by health professionals. Case reports sent in by health professionals were examined in more detail and showed a range of menstrual abnormalities with varying degrees of severity, some of which require intervention or additional diagnostics. Overall, most case reports originated from the age group of 25–34 years (37.6%) and the age group of 35–44 years (27.9%). The majority of women had a BMI of 18.0–24.9 kg/m^2 (60.2%). Amenorrhoea/oligomenorrhoea was the most reported menstrual abnormality (33.3%), followed by heavy menstrual bleeding (29.4%) and irregular blood loss (22.7%) with no substantial differences between vaccines. In total, 38 case reports of menstrual abnormalities were considered serious by the reporter according to the CIOMS criteria. About half of the menstrual abnormalities sent in through the spontaneous reporting system were not resolved at time of reporting, while ~25–40% of the abnormalities were resolved or resolving (data not shown).

The reporting rates per age group were calculated for the 4 vaccines (Table 2). Calculations and number of administered vaccine doses are shown in Tables S2–S5. Overall, the reporting rates for all menstrual abnormalities together were highest for the Johnson & Johnson vaccine (523.0 per 100 000 vaccinations). In general, the rates were high (>150 reports per 100 000 vaccinations) for all first and second doses in the age groups younger than 45 years. The reporting rate was the highest for the age group 25–34 years, except for the Johnson & Johnson vaccine.

3.1.1 | Amenorrhoea

Within the amenorrhoea/oligomenorrhoea category, 4065 case reports concerned amenorrhoea following COVID-19 vaccination (Table S6), of which the majority received the Pfizer vaccine (80.5%). In total, there were 3 amenorrhoea case reports that were considered serious according to the CIOMS criterion of 'Other Important Criteria'. Cases include a 17-year-old woman with amenorrhoea, which lasted for 7 months and required gynaecological examination. Dose of vaccination, reporter and age of the vaccinee did not differ much from all menstrual disorders combined (Table 1). The majority of women (79.0%) had not recovered at the time of reporting, while 7.3% did recover and 3.7% were recovering at the time of reporting. Out of 298 women who recovered, 149 (50.0%) reported that their menstruation was delayed for >4 days. For part of the amenorrhoea cases, we received more detailed information about the adverse effect and the outcome. For women with amenorrhoea, the timing of vaccination in relation to the menstrual cycle was also a point of interest. Forty-five out of 64 women (70.3%) noted to be in the second half of their menstrual cycle (i.e. postovulation) at time of vaccination. Eighty-four women provided information about which cycles were abnormal, most of these women (91.7%, $n = 77$) reported that the first menstruation after vaccination was absent, and for the remaining women (8.3%, $n = 7$), the first menstrual cycle after vaccination was normal, but the menstruation was absent in the second cycle. For the amenorrhoea cases, there were 32 so-called rechallenge cases known; women who received the second dose of vaccination after experiencing absence of menstruation following the first dose of vaccination. Of these, 13 women noted recurrence of amenorrhoea after the second dose, 5 did not, and for 14 women, these data were unknown. Lastly, from the women who provided additional information, 12 consulted their general practitioner, and 5 consulted their gynaecologist. The predominant reason for consultation of a doctor was an exceptionally long absence of menstruation; for example, a woman in her 20s–30s with a child wish indicated her menstrual cycle being absent for 2.5 months while not being recovered at the time of reporting. Additional testing did not show any abnormalities. Another example concerned a woman of 30–40 years who indicated absence of menstruation during 8 months following vaccination, and she had not recovered at the time of reporting. Also in this case, additional testing

TABLE 1 Overview of spontaneous menstrual abnormality case reports.

	AstraZeneca (%)	Johnson & Johnson (%)	Moderna (%)	Pfizer (%)	Unknown vaccine brand (%)	Total (%)
No. reports	614	1647	2727	19 079	23	24 090
No. different AEFIs at PT level	2079	5342	10 977	53 978	57	72 433
No. serious menstrual PTs	7 (1.1)	1 (0.1)	5 (0.2)	25 (0.1)	0	38 (0.2)
Prior COVID-19 infection	123 (20.0)	318 (19.3)	518 (19.0)	3866 (19.3)	5 (21.7)	4650 (19.3)
Dose of vaccination						
First	281 (45.8)	1642 (99.7)	1061 (38.9)	8638 (45.3)	13 (56.5)	11 635 (48.3)
Second	333 (54.2)	5 (0.3)	1476 (54.1)	9506 (49.8)	6 (26.1)	11 326 (47.0)
Third	0	0	190 (7.0)	935 (4.9)	4 (17.4)	1129 (4.7)
Reporter						
Consumer	606 (98.7)	1638 (99.5)	2720 (99.7)	18 973 (99.4)	21 (91.3)	23 958 (99.5)
Health professional	8 (1.3)	9 (0.5)	7 (0.3)	106 (0.6)	2 (8.7)	132 (0.5)
Age						
<25 years	82 (13.4)	387 (23.5)	357 (13.1)	3303 (17.3)	5 (21.7)	4133 (17.2)
25–34 years	224 (36.5)	560 (34.0)	808 (29.6)	7466 (39.1)	10 (43.5)	9067 (37.6)
35–44 years	174 (28.3)	351 (21.3)	808 (29.6)	5382 (28.2)	4 (17.4)	6718 (27.9)
45–54 years	107 (17.4)	345 (20.9)	712 (26.1)	2782 (14.6)	4 (17.4)	3949 (16.4)
55–64 years[a]	25 (4.1)	8 (0.5)	37 (1.4)	121 (0.6)	0	190 (0.8)
≥65 years[a]	2 (0.3)	1 (0.1)	5 (0.2)	22 (0.1)	0	29 (0.1)
Unknown	0	1 (0.1)	0	9 (0.0)	0	10 (0.0)
BMI (kg/m^2)						
<18.0	4 (0.7)	25 (1.5)	31 (1.1)	329 (1.7)	0	389 (1.6)
18.0–24.9	296 (48.2)	1046 (63.5)	1636 (60.0)	11 509 (60.3)	14 (60.9)	14 501 (60.2)
25.0–29.9	150 (24.4)	395 (24.0)	665 (24.4)	4586 (24.0)	7 (30.4)	5803 (24.1)
≥30.0	144 (23.5)	152 (9.2)	337 (12.4)	2185 (11.5)	1 (4.3)	2819 (11.7)
Unknown	20 (3.3)	29 (1.8)	58 (2.1)	470 (2.5)	0	578 (2.4)
Menstrual abnormality[b]						
Amenorrhoea/oligomenorrhoea	198 (32.2)	473 (28.7)	859 (31.5)	6478 (34.0)	6 (26.1)	8014 (33.3)
Dysmenorrhoea	66 (10.7)	223 (13.5)	316 (11.6)	2462 (12.9)	1 (4.3)	3068 (12.7)
Heavy menstrual blood loss	178 (29.0)	518 (31.5)	818 (30.0)	5559 (29.1)	9 (39.1)	7082 (29.4)
Intermenstrual blood loss	106 (17.3)	336 (20.4)	480 (17.6)	3585 (18.8)	6 (26.1)	4513 (18.7)
Irregular blood loss	130 (21.2)	396 (24.0)	642 (23.5)	4303 (22.6)	4 (17.4)	5475 (22.7)
Less menstrual blood loss	23 (3.7)	55 (3.3)	91 (3.6)	680 (3.6)	0	849 (3.5)
Withdrawal blood loss abnormal	8 (1.3)	30 (1.8)	25 (0.9)	242 (1.3)	0	305 (1.3)
Other	3 (13.0)	438 (16.1)	248 (15.1)	112 (18.2)	2641 (13.8)	3342 (14.3)

Abbreviations: BMI, body mass index; PT, preferred term.
[a]Data as reported, symptoms might be related to menopause as well.
[b]Women can report menstrual disorders from multiple categories in 1 report.

did not result in finding a cause. The follow-up questions sent to women who reported amenorrhoea included a question about the use of hormonal contraception. For 140 women, the use of hormonal contraception was known, yet there were no substantial differences between hormonal contraceptive users and nonusers other than age; hormonal contraception users were younger than nonusers (Table S7).

3.1.2 | Heavy menstrual bleeding

A total of 7068 women sent in a case report of heavy menstrual bleeding, of which the majority followed Pfizer vaccination (78.0%; Table S8). Of these, 47 case reports were considered serious according to the CIOMS criteria, and this set included 21 menstrual events

TABLE 2 Reporting rates per 100 000 vaccinations by vaccine brand and dose.

	<25 years	25–34 years	35–44 years	45–54 years	55–64 years	≥65 years	Total
AstraZeneca							
First dose	174.7	352.9	195.1	72.5	1.8	0.7	40.8
Second dose	241.8	441.9	245.2	91.1	3.9	0.7	52.1
Johnson & Johnson							
First dose	575.7	1091.6	1149.5	185.5	17.2	0.0	523.0
Moderna							
First dose	309.4	553.9	273.2	134.1	1.1	2.6	213.3
Second dose	407.1	664.7	490.2	261.8	10.7	0.0	319.6
Third dose	[a]	[a]	[a]	31.9	2.6	0.3	8.7
Pfizer							
First dose	206.3	636.9	331.4	143.7	4.8	0.4	177.8
Second dose	223.0	689.5	471.3	224.0	8.9	0.8	210.0
Third dose	35.5	81.8	62.9	46.0	2.9	0.2	40.4

[a]Reporting rate not displayed due to sample size constraints (risk of subject identification).

that were recorded as serious at the time of reporting. Six women reported hospitalization. These included the case of woman aged 25 years who reported menstrual bleeding lasting for 3 months, leading to anaemia, which required hospitalization. An ultrasound was made, and the patient was treated with a blood transfusion, ferrous fumarate and tranexamic acid. Other menstrual events were reported as CIOMS seriousness 'Life-threatening' ($n = 6$), 'Disabling' ($n = 3$) and 'Other'. Among the cases listed as life-threatening was a 24-year-old women with a factor VII Leiden deficiency who had not menstruated for 9 years due to placement of an intrauterine device and who reported severe menstrual bleeding after both her first and second vaccination. As treatment, coagulants were given. Most women were aged 25–34 years (33.9%), followed by 35–44 years (31.4%), which is in line with the overall age of women who reported the menstrual abnormalities (Table 1). About half of the women (54.8%) had not recovered at the time of reporting, 23.0% had recovered, and 13.5% were recovering at the time of reporting. For those who recovered before reporting, 212 (67.9%) had a duration of bleeding of <14 days. The majority of women with heavy menstrual bleeding for which detailed information was available (65.4%, $n = 138/211$) were vaccinated in the second half of their menstrual cycle. The first menstrual cycle after vaccination was abnormal in 222 out of 246 (70.6%) women, whereas 24 women indicated the heavy menstrual bleeding was not yet present in the first cycle. Information about the extent of change of menstrual blood loss was retrieved from 422 women: blood loss was 'more than twice as much' in 298 women (70.6%), 'twice as much' in 100 women (23.7%) and 'a little more' in 24 women (5.7%). Of all cases, 112 were rechallenge cases who received the second dose of vaccination. Half of these women (50.8%) experienced the same complaints after the second dose. Consultation of the general practitioner and the gynaecologist was indicated by 58 and 25 women, respectively, whereas 3 women were hospitalized due to the complaints. Examples of cases who consulted a physician included a woman of 50–60 years who was vaccinated at the end of her period and started bleeding again for another week. A blood test and uterine ultrasound revealed no abnormalities. Another woman in her 30s–40s presented with persistent menstrual blood loss of 14 days requiring a hormonal treatment to terminate the bleeding. Some women consulted the physician due to their medical history, for example, a 20- to 30-year-old woman with factor VII deficiency who usually does not bleed because of her intrauterine device. Six hours after the first vaccination, she started bleeding and needed treatment to stop the vaginal blood loss. This recurred after the second vaccination. In 462 out of the 7068 case reports received, women indicated the use of hormonal contraceptives (Table S9), and 37 women reported the use of an antithrombotic drug as concomitant medication. Women with heavy menstrual bleeding using hormonal contraception were generally younger than women who did not use this type of contraception (means: 32 *vs*. 38 years). Moreover, women who were using hormonal contraception experienced heavier and longer menstrual blood loss compared to nonusers.

3.2 | CEM study

3.2.1 | Cohort description

A total 16 929 female vaccinees (age ≥16 years) completed the baseline questionnaire and at least 1 of the follow-up questionnaires about the presence of AEFIs (Figure 1). Of these 16 929 women, 13 573 (80.2%) were <65 years. During the study period, 432 women (all aged <65 years) recorded 1 or multiple menstrual abnormalities in the follow-up questionnaires (Figure 1). This corresponds to an incidence of 31.8 per 1000 women aged <65 years and 41.1 per 1000 women aged ≤54 years. Table 3 displays the number of women who recorded a menstrual abnormality by vaccine brand and age group along with the incidence in the total CEM cohort. Overall, the incidence of menstrual abnormalities was highest in women who received the Pfizer

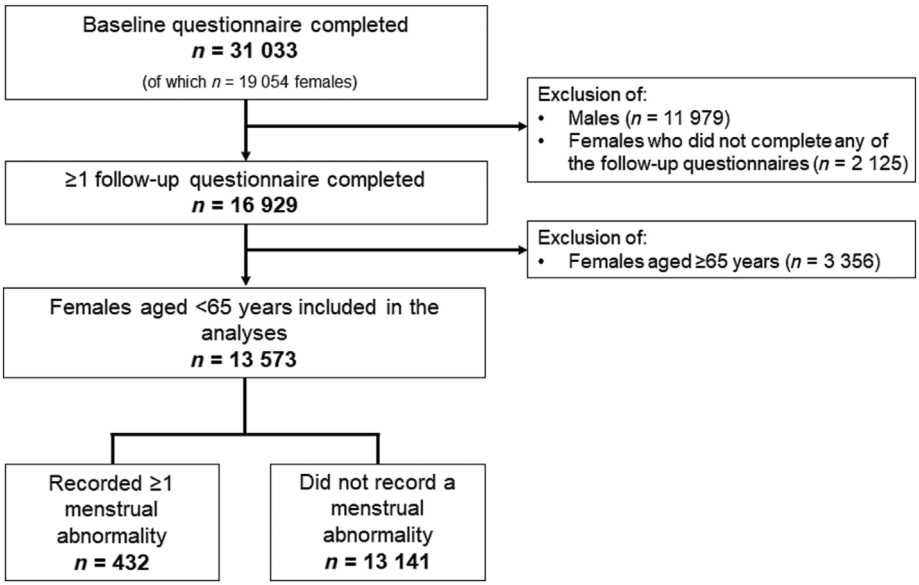

FIGURE 1 Flow chart of the data management process in the cohort event monitoring study.

	AstraZeneca		Johnson & Johnson		Moderna		Pfizer		Total	
Age (years)	*N*	Inc	*N*	Inc	*N*	Inc	*N*	Inc	*N*	Inc
<25	4	7.2	8	67.2	6	45.1	8	31.9	26	24.6
25–34	34	30.2	12	41.1	27	64.3	71	97.5	144	56.1
35–44	46	32.3	17	54.1	33	59.7	43	75.3	139	48.6
45–54	32	17.4	26	30.3	38	50.3	21	50.4	117	30.2
55–64 [a]	3	1.3	0	-	1	2.6	2	5.4	6	1.9
Total	119	16.4	63	36.0	105	46.9	145	62.1	432	31.8

TABLE 3 Number and incidence (per 1000 vaccinated women) of recorded menstrual abnormalities among women 16–64 years in the CEM study.

Abbreviations: Inc. incidence; N, number of women who recorded at least 1 menstrual abnormality in the follow-up questionnaires.

[a]As reported in the questionnaires, symptoms might also be related to menopause.

vaccine. Mean ages of the women who recorded a menstrual abnormality ranged from 34.7 to 39.6 years for the different vaccine brands.

Some women recorded >1 menstrual abnormality, leading to a total of 552 observations (Figure 2A and Table S10). Heavy menstrual bleeding, amenorrhoea/oligomenorrhoea and irregular blood loss were the most recorded menstrual abnormalities in the CEM study (Figure 2A). The incidences of amenorrhoea/oligomenorrhoea and irregular blood loss exceeded 10 per 1000 vaccinated women (aged <65 years) for Johnson & Johnson, Moderna and Pfizer vaccines, while the incidence of heavy menstrual bleeding exceeded 10 per 1000 vaccinated women only for the Moderna and Pfizer vaccines (Figure 2B). Multivariable logistic regression on the occurrence of any menstrual abnormality in women aged ≤54 years showed significant increased odds for the Johnson & Johnson vaccine (odds ratio [OR] 1.83; 95% confidence interval [CI] 1.33–2.49), Moderna vaccine (OR 2.44; 95% CI 1.86–3.20) and Pfizer vaccine (OR 3.04; 95% CI 2.36–3.93) as compared to the AstraZeneca vaccine, when adjusted for age (Table S11). For all 8 menstrual abnormality categories, the incidences were highest in the age groups of 25–34 and 34–44 years (Figure 2B). When adjusted for vaccine brand, this resulted in significantly increased ORs of the occurrence of any menstrual abnormality of 2.18 and 2.01 for the age groups of 25–34 and 35–44 years, respectively (Table S11). We observed a tendency towards reduced risk of menstrual abnormalities with increasing BMI levels, although none were significant (Figure 2B and Table S11). No significant association was observed for SARS-CoV-2 infection prior to vaccination (Figure 2B and Table S11), nor for any of the studied comorbidities except psychological disorders (Table S11). For the women who indicated the presence of an underlying psychological disorder, the ORs were significantly increased for amenorrhoea/oligomenorrhoea (OR 2.08; 95% CI 1.14–3.50), intermenstrual blood loss (OR 3.01; 95% CI 1.50–5.50) and irregular blood loss (OR 2.41; 95% CI 1.28–4.17), adjusted for age and vaccine brand (data not shown). This could not be attributed to the reported use of any comedication.

Most menstrual abnormalities (63.8%, $n = 352$) occurred after the second dose of vaccination, while 200 (36.2%) menstrual abnormalities occurred after the first dose (for $n = 146$ of these, no second dose of vaccination was registered, including $n = 78$ observations recorded by women who received the Johnson & Johnson vaccine). The median TTO for the menstrual abnormalities was 14 days (interquartile range [IQR] 5–30 days). The lowest TTOs were recorded for intermenstrual blood loss and withdrawal blood loss (median 10 and

FIGURE 2 Absolute numbers (A), incidence per 1000 female participants (aged <65 years; B) and time to onset and time to resolve (C) of recorded menstrual abnormalities by category. *Not restricted to 1 recorded adverse event following immunization within 1 menstrual abnormality category. **Restricted to 1 recorded adverse event following immunization within 1 menstrual abnormality category.

11 days, respectively), while for the other menstrual abnormalities, the median TTOs ranged between 12.5 and 18.5 days (Figure 2C). TTR was recorded for half of the menstrual abnormalities ($n = 280$), while for the remaining observations, the complaint was not yet resolved before the end of follow-up (defined by either the end of study [$n = 211$], loss to follow-up [$n = 59$] or incorrectly specified TTR [$n = 2$]). Overall, median TTR of the menstrual abnormalities was 7 days (IQR 4–14 days), with a higher TTR for amenorrhoea/oligomenorrhoea (median 11 days; IQR 5–30 days; Figure 2C). Overall, most women experienced the menstrual abnormality as slightly burdensome (39.5%; Table S12). Dysmenorrhoea and heavy menstrual bleeding were perceived as extremely burdensome by 17.6 and 15.1% of women, respectively, which was higher than for the other menstrual abnormalities. By contrast, less menstrual blood loss and abnormal withdrawal blood loss were associated with a lower perceived burden.

3.2.2 | Corecorded adverse drug reactions

Menstrual abnormalities were commonly recorded along with other AEFIs. The most corecorded AEFIs were systemic of nature such as fatigue, headache, malaise and myalgia, which correspond to the overall most frequently recorded AEFIs after COVID-19 vaccination (Figure S2). While the majority of menstrual abnormalities presented after the second dose of vaccination, most corecorded AEFIs were attributable to the first dose of vaccination. AEFIs that are menstrual symptoms as well such as breast complaints (pain, swelling, tenderness), mood swings, depressed mood, hot flushes and back pain, were only to a limited extent corecorded with menstrual abnormalities (Figure S2).

3.2.3 | Multiple menstrual abnormalities at individual level

Overall, 79 women recorded > 1 menstrual abnormality (based on the 8 aforementioned categories). These include either the same type of menstrual abnormality twice, attributable to 2 distinct doses of vaccination, and/or ≥2 distinct menstrual abnormalities (attributable to the same dose or 2 different doses). Within the same dose, the most commonly corecorded menstrual abnormalities were irregular blood loss and heavy menstrual bleeding (first dose $n = 9$; second dose $n = 16$) and amenorrhoea/oligomenorrhoea and heavy menstrual bleeding (first dose $n = 1$; second dose $n = 12$). The combination of irregular and heavy menstrual bleeding was recorded in equal numbers by recipients of the AstraZeneca, Moderna and Pfizer vaccine ($n = 7$, 8 and 8, respectively), whereas the combination of amenorrhoea/oligomenorrhoea was predominantly recorded after receiving the Pfizer vaccine ($n = 6$). One woman recorded heavy menstrual bleeding after both doses of vaccination, and 1 woman reported intermenstrual bleeding after both doses of vaccination; both women received the Pfizer vaccine.

3.2.4 | Use of contraceptives

We assessed a possible association between occurrence of a menstrual abnormality and the use of contraceptives. Table 4 displays the numbers of women who recorded a menstrual abnormality by menstrual abnormality category and type of contraceptive use. The ORs of experiencing any menstrual abnormality were 2.59 (95% CI 1.28–4.73) and 0.66 (95% CI 0.43–0.96) in women who used topical hormonal contraceptives and hormonal contraceptives, respectively, as compared to women who did not report the use of any hormonal contraceptives when adjusting for age and vaccine brand (data not shown). The OR was particularly high for intermenstrual blood loss when comparing the use of any of 2 categories hormonal contraceptives to no use of hormonal contraceptives, adjusted for age and vaccine (OR 4.70; 95% CI 2.78–7.81), although numbers are low. Overall, no association was observed between the use of hormonal contraceptives and the perceived burden of the menstrual abnormalities.

4 | DISCUSSION

Several months after the vaccination of younger age groups against COVID-19, reports of menstrual abnormalities appeared, varying

TABLE 4 Number and percentage of hormonal contraception use by women who recorded menstrual abnormalities.

	No contraceptives reported		Hormonal contraceptives		Topical use hormonal contraceptives	
	N	%	*N*	%	*N*	%
Any menstrual abnormality	393	91.0	28	6.5	11	2.5
Amenorrhoea/oligomenorrhoea	130	97.0	3	2.2	1	0.7
Dysmenorrhoea	31	91.2	0		0	
Heavy menstrual bleeding	118	84.9	6	4.3	3	2.2
Intermenstrual blood loss	50	60.2	18	21.7	8	9.6
Irregular blood loss	107	95.5	1	0.9	1	0.9
Less menstrual blood loss	22	100.0	0		0	
Withdrawal blood loss abnormal	3	75.0	1	25.0	0	
Other	24	100.0	0		0	

from heavy menstrual bleeding, absence of blood loss, a deregulated menstrual cycle and abnormalities in withdrawal bleeding. In this study, we summarize the reports of menstrual abnormalities received by the Netherlands Pharmacovigilance Centre Lareb from the beginning of 2021 until the end of March 2022. Over 24 000 case reports of menstrual abnormalities were received through the spontaneous reporting system, and over 500 menstrual abnormalities were recorded by participants in the CEM study. Of all 8 categories of menstrual abnormalities assessed, amenorrhoea/oligomenorrhoea and heavy menstrual bleeding collectively accounted about half of all abnormalities reported. The majority of the received records of menstrual abnormalities were associated with the Pfizer vaccine in both the spontaneous case reports (79.2%) and the CEM study (34.6%), which is also the mainly distributed vaccine in the Netherlands. Overall, there were no large differences between vaccine brands with respect to the characteristics of the case reports such as the reporter, age groups, BMI and menstrual abnormality categories. Although the AstraZeneca vaccine has been associated with high incidences of other kinds of adverse reactions as compared to the other vaccine brands, the incidence of menstrual abnormalities is rather low for the AstraZeneca vaccine in the spontaneous reporting and the CEM study. A higher prevalence of menstrual abnormalities among Pfizer recipients compared to AstraZeneca recipients was also observed among Arab women (49.3 *vs*. 21.1%).[33] The reporting rates based on the spontaneous reports from our study, however, showed that the Johnson & Johnson vaccine had the highest reporting rates compared to the other vaccine brands: overall, 523.0 reports of menstrual abnormalities per 100 000 administered vaccines. This corresponds to a ratio of 1 in 200 female recipients of the Johnson & Johnson vaccine who reported a menstrual abnormality to Lareb. Several studies have examined the effect of COVID-19 vaccination on the menstrual cycle (length) and/or menses.[25,34] Nazir et al. summarized the methodological aspects and main outcomes of 14 studies in a systematic review, most of which had a cross-sectional design.[25] Among the included studies, heavy menstrual bleeding, intermenstrual blood loss and irregular blood loss were most commonly reported. Several studies provided percentages of women who reported specific menstrual abnormalities including heavy menstrual bleeding ($n = 8$ studies; 0.2–66.7%; median 19.5%), irregular blood loss ($n = 5$; 0.0–60.5%; median 10.8%), intermenstrual blood loss ($n = 4$; 0.3–12.7%; median 2.2%), dysmenorrhoea ($n = 3$; 14.6–62.4%; median 21.3%), amenorrhoea/oligomenorrhoea ($n = 2$; 12.6 and 30.4%) and less menstrual blood loss ($n = 2$; 0.0–36.8%; median 11.1%).[23–25,35–40] The large spread in percentage between the studies could be the result of differences in age cut-offs used (i.e. some only included women aged 18–45 years) as also in our cohort, the incidence differed strongly by age for some menstrual abnormalities (Figure 2). Two studies performed disproportionality analyses on data from spontaneous reports to quantify the excess reported menstrual abnormalities after COVID-19 vaccination, resulting in a reporting OR of 7.83 (95% CI 7.39–8.28) for menstrual abnormalities.[40,41] Edelman et al. concluded based on data from several countries that menstrual cycle length was temporarily affected by vaccination only to a limited extent, regardless of the type of COVID-19 vaccine (i.e. mRNA or vector vaccine), while the menses length was not affected at all.[34] These results suggest that a biological link between COVID-19 vaccination and menstrual abnormalities is plausible. It has been suggested that the systemic immune response might interfere in many pathways that are involved in the menstrual cycle.[42] These include, for example, hormonal and inflammatory pathways. Also, evidence suggests that the number of certain immune cells as well as their activity differs between the first and second part of the menstrual cycle.[43] In this light, it is an interesting finding that most menstrual abnormalities were found in women who were vaccinated in the second part of their menstrual cycle, after ovulation. In the CEM study, we observed a decreased odds of having a menstrual abnormality when using hormonal contraceptives. Results from a British cohort study suggested that the use of hormonal contraception might mediate the effects of vaccination on the menstrual cycle length[44]; unfortunately, the sample size of our CEM study did not allow to assess the effects of hormonal contraception on the incidence of the different menstrual abnormalities. It is assumable that this finding is due to the prevention of proliferation of the endometrium and ovulation caused by oral contraceptives, and thus, an immune response would have less influence on the bleeding pattern. We did not observe a clear pattern between menstrual abnormalities and coreported AEFIs other than a high degree of coreporting of the most common AEFIs after COVID-19 vaccination. Presence of comorbidities showed a significant association between psychological disorders and the occurrence of menstrual abnormalities, in particular amenorrhoea/oligomenorrhoea and intermenstrual/irregular blood loss, which is an interesting finding that might signal a different pathway than just the immune response. Moreover, it was also questioned whether the observed menstrual abnormalities could have been the result of pandemic-related stress rather than vaccination.[8] In a previous CEM study investigating biological medicines, psychiatric comorbidities were associated with higher burden of adverse drug reactions in participants.[45]

This study comes with several limitations in both the spontaneous reporting system and the CEM study. Following the massive vaccination campaigns worldwide against COVID-19 infection, there has been extensive (social) media coverage about several specific possible adverse effects of the different vaccines. It is well known that media attention can have extensive effects of the reporting pattern in spontaneous reporting systems.[46–48] However, for menstrual abnormalities in particular, disentangling the true possible causal effect of vaccination on the menstrual abnormalities and the effect of media-attention was challenging as, for most of the abnormalities, the background incidence (i.e. regardless of COVID-19 vaccination or infection) is not/partially known. In the Netherlands, the first reports in the national mainstream media about the possible association between COVID-19 vaccination and menstrual abnormalities date back to the first week of July 2021, while Lareb received the first case reports of menstrual abnormalities already in February 2021. The widespread media attention has led to a significant temporary increase in spontaneous case reports of menstrual abnormalities;

however, the dates of onset lack a pattern of media attention and seem to correlate with the Dutch vaccination programme (Figure S2). Similarly, in the CEM study, an increase in reported menstrual abnormalities was observed around July 2021, which is presumably partially attributable to the media attention (Figure S3). Nonetheless, similar trends were observed in the CEM-study, which is (due to its prospective design) only to a minor extent suffering from these limitations. Detailed clinical information about the menstrual abnormality was lacking in most case reports, even though the reporting system allows women to give a comprehensive description of the deviating aspects of their menstrual cycle. Also, in the CEM-study, we were unable to retrieve additional clinical details about the menstrual abnormality, for instance, about the timing of vaccination in the menstrual cycle, which was suggested to impact the observed menstrual abnormalities in literature.[39,44,49] For the serious menstrual disorders, it should be noted that we included the seriousness category 'Other', which is somewhat subjective. For the case reports on heavy menstrual bleeding, 4 reports were re-coded in the Lareb database as nonserious after this study. Although the case reports were listed as serious, this does not imply there is a certain causal relationship in all reports. Some literature suggests that SARS-CoV-2 infection can cause menstrual abnormalities as well.[26,50] While we retrieved information about the occurrence of a confirmed SARS-CoV-2 infection prior to vaccination, subclinical infections and infections that occurred shortly after vaccination could not be taken into account in this study. In both data sources in this study, the use of hormonal contraceptives is to a certain extent underreported as in the questionnaires women were expected to list the use of hormonal contraceptives as part of the comedication rather than a through targeted question about hormonal contraceptive use. In the Netherlands, 1.4 million women used a hormonal contraceptive in 2021,[51] corresponding to 30–35% of women of reproductive-age. In contrast, in the CEM-study, ~12% of the women in the same age range reported the use of hormonal contraceptives. This might hamper the interpretation of the observed associations. Overall, virtually nothing is documented about the incidence of menstrual abnormalities in the Dutch population (i.e. regardless of COVID-19 vaccination), which hampers estimations on the magnitude of excess menstrual abnormalities in vaccinated women. Disproportionality analysis was not feasible for the Dutch spontaneous reporting system due to the large volume of reported AEFIs for the COVID-19 vaccines and selective reporting for certain AEFI.[40,41,52]

In conclusion, this Dutch CEM study found an incidence of menstrual disorders of 41.4 per 1000 female participants aged ≤54 years. This was complemented with the analysis of >24 000 case reports received through the spontaneous reporting system in the Netherlands. Based on these 2 data sources and literature, a relationship between COVID-19 vaccination and the occurrence of menstrual disorders seems plausible. Further studies are needed to elucidate the mechanism of these adverse reactions, the possible risk factors thereof and the effect of timing of vaccination in the menstrual cycle on both the immune response and the occurrence of AEFIs.

AUTHOR CONTRIBUTIONS

The original study protocol was designed by F. van Hunsel. Data analysis was performed by J. W. Duijster. The design of the article was determined by all authors. All authors contributed to the final data analysis and to manuscript drafting and revision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as Supporting Information. The datasets for this manuscript are not publicly available because of the data protection policy of the Netherlands Pharmacovigilance Centre Lareb. Requests to access the datasets should be directed to the first author and will be granted on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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