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Heavy bleeding and other menstrual disturbances in young women after COVID-19 vaccination

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ABSTRACT

Background: Many signals of menstrual disturbances as possible side effects of vaccination against COVID-19 have been reported. Our objective was to compare the risk of menstrual disturbances before and after vaccination among women aged 18–30 years in Oslo, Norway.

Methods: We used electronic questionnaires to collect reports of menstrual disturbances from 3972 women aged 18–30 years, participating in the population-based Norwegian Young Adult Cohort. We examined the occurrence of menstrual disturbances (heavier bleeding than usual, prolonged bleeding, shorter interval between menstruations, longer interval between menstruations, spot bleedings, stronger pain during menstruation, period pain without bleeding) before and after the first and second dose of COVID-19 vaccine. Relative risks (RR) according to vaccination were estimated using a self-controlled case-series design. We performed additional analyses stratified by vaccine brand, contraception/hormone use, and presence of gynecological condition(s).

Results: The prevalence of any menstrual disturbance was 36.7 % in the last menstrual cycle prior the first vaccine dose. The RR for heavier bleeding than usual was 1.90 (95 % CI: 1.69–2.13) after the first vaccine dose and 1.84 (95 % CI 1.66–2.03) after the second dose. Increased risks of prolonged bleeding, shorter interval between menstruations, and stronger pain during menstruation were also observed after both doses. The RRs did not differ with vaccine brand, contraception/hormone use, or presence of gynecological condition(s) for any of the menstrual disturbances.

Conclusion: Menstrual disturbances were common regardless of vaccination. We found increased risk of menstrual disturbances after vaccination, particularly for heavier bleeding than usual, prolonged bleeding, shorter interval between menstruations, and stronger period pain. In the future, menstrual characteristics should be included in vaccine trials.

1. Introduction

Previously unforeseen signals of menstrual disturbances as possible side effects of the COVID-19 vaccines have been reported to spontaneous reporting systems in many countries, including Norway [1]. By 23 November 2022, the UK Yellow Card system had received more than 50 000 reports of menstrual disorders including heavier than usual periods, delayed periods and unexpected vaginal bleeding, after COVID-19 vaccination [2].

To date, a number of studies have been conducted to evaluate the potential association between COVID-19 vaccination and menstrual disturbances [3–21]. Many studies report menstrual disturbances at high frequencies after vaccination [4,5,8,10,21], and interval changes have been more commonly observed among vaccinated individuals by use of data from cycle tracking applications [17,18,22]. However, since most studies are retrospective using non-random recruitment forms, for instance social media platforms, the representativeness have been questioned. Preliminary analyses from the current study were therefore considered important evidence in the safety assessment conducted by the Pharmacovigilance Assessment Committee (PRAC) for the European Medicines Agency (EMA). In a statement issued in October 2022, PRAC concluded that there is at least a reasonable possibility of a causal association between COVID-19 vaccination and heavy menstrual bleeding. They recommended that heavy menstrual bleeding should be included in the product information of the mRNA vaccines as a possible side effect [23].

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Using an ongoing population-based cohort of young adults in Oslo, Norway, questions on menstrual disturbances were included in the electronic questionnaires in the early fall of 2021. We have studied the prevalence of heavy menstrual bleeding and other menstrual disturbances before and after vaccination. The richness of the dataset allowed for additional analyses in subgroups defined by regular cycle lengths and bleeding patterns, previous gynecological conditions, and contraception or hormone use.

2. Methods

2.1. Study population

From May to August 2021, 46 234 men and 51 074 women, aged 18–30 years, registered in the National Population Registry as living in Oslo, were randomly invited to The Young Adult Cohort. The aim of the cohort is to study short- and long-term consequences of the COVID-19 pandemic, including effects of infection, vaccination and public health interventions using repeated questionnaire surveys, and for some participants, blood sampling. In total, 12 623 subjects (13 %), 8576 women (17 %) and 4281 men (9 %), consented electronically to participate in the cohort. The study was approved by the Regional Ethics Committee South East Norway, no. 229359. Written informed consent was obtained from all participants.

For the present study, we used information from female participants responding to the electronic questionnaire distributed to all participants in the Young Adult Cohort in late October 2021 (questionnaire no.4). At this time, most participants had received two doses of COVID-19 vaccine. Of the 8576 women in the cohort, 5765 women returned this questionnaire, corresponding to a response rate of 67 % (Fig. 1).

We excluded 41 women who had received three vaccine doses, 27 women with inconsistency between self-reported vaccination and registry information, 1634 women who reported not to menstruate and 66 unvaccinated women. In addition, 16 women who received the first vaccine dose less than 6 weeks prior to filling in the questionnaire were excluded to allow for at least one menstrual cycle after vaccination, leaving 3972 women *for analysis of menstrual disturbance after the first vaccine dose* (first dose study sample) (Fig. 1). *For analysis of menstrual disturbances after the second dose,* we included the 3507 women that had received two vaccine doses at least 6 weeks prior to filling in the questionnaire (second dose study sample) (Fig. 1).

2.2. Variables

2.2.1. Vaccination

Information on date of vaccination and type of vaccine was obtained through linkage to the National Immunisation Registry (SYSVAK) [24], using unique personal identification numbers. In Norway, most vaccinees received the mRNA vaccines Comirnaty (Pfizer/BioNTech; BNT162b2), or Spikevax (Moderna; mRNA-1273) or a combination of the two. The adenovector-based vaccine Vaxzevria (AstraZeneca; ChAdOx nCoV-19; AZD1222) was only offered through the programme until March 2021 [25].

2.2.2. COVID-19

Information on laboratory polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infections was obtained by linkage to the National Surveillance System for Communicable Diseases (MSIS).

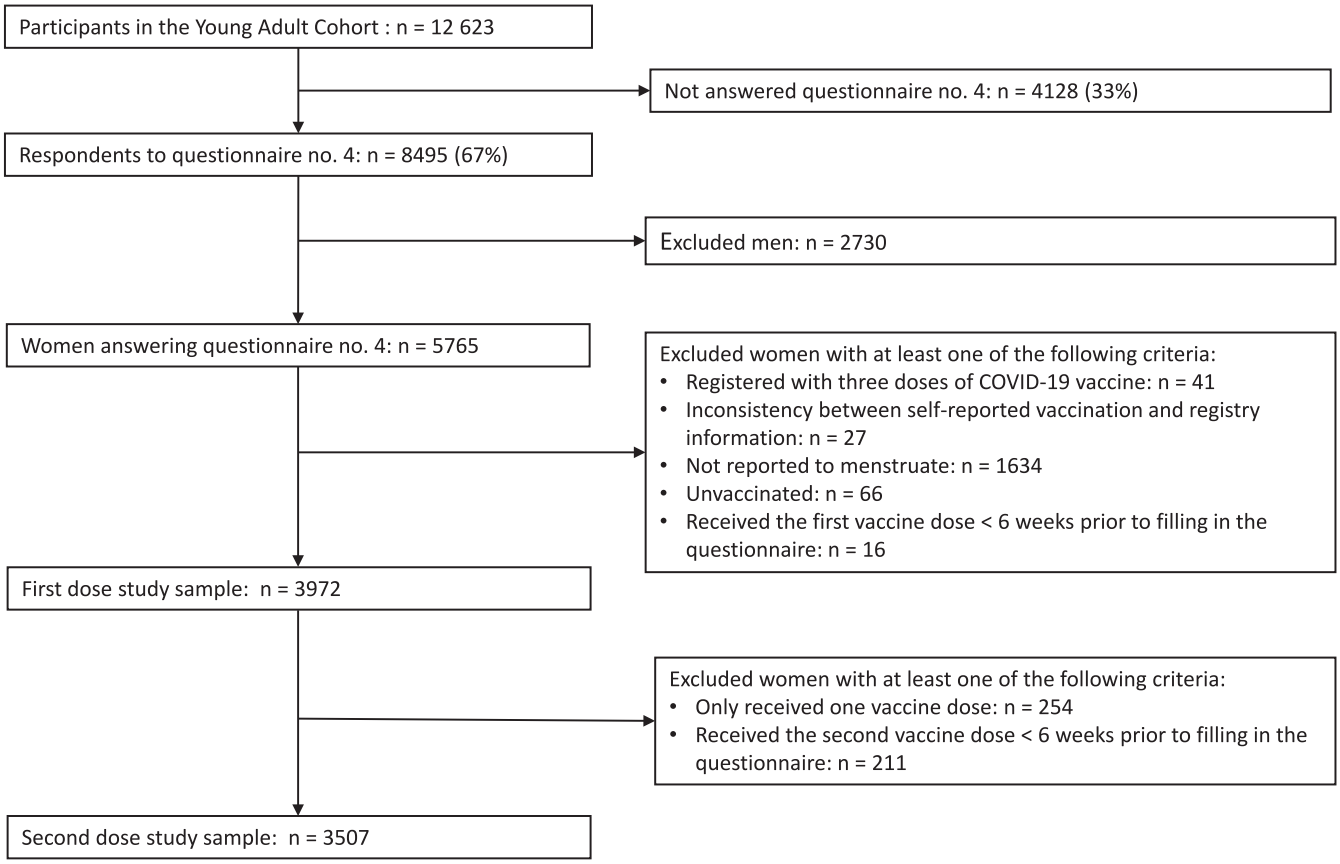

Fig. 1. Flowchart of inclusion and study samples.

2.2.3. Menstrual symptoms/ patterns

In the questionnaire distributed in late October, vaccinated, menstruating women were asked whether they had experienced any of the following disturbances in their last menstrual cycle before the first vaccine dose: 1) heavier bleeding than usual, 2) prolonged bleeding, 3) shorter interval between menstruations than usual, 4) longer interval between menstruations than usual, 4) spot bleedings between menstruations, 5) stronger pain during menstruation than usual, and 6) period pain without bleeding. The same list of questions applied for their first menstrual cycle after the first vaccine dose, their last cycle before the second vaccine dose, and their first cycle after the second dose.

Self-reported information on the usual bleeding pattern and menstrual cycle, previous gynecological conditions and use of contraception/hormone treatment was retrieved from two previous questionnaires (distributed in September 2021). Information on contraception and hormone use was based on the following question "Do you currently use contraception, hormone replacement therapy to relieve symptoms of the menopause, or other hormone treatment? Women who answered "Yes", were asked to select the appropriate category/categories as follows: combination pill, progesterone only pill, contraceptive implant, copper intrauterine device (IUD), hormonal IUD, other contraception, hormone replacement therapy (HRT), and other hormone treatment. Information on active tracking of the menstrual cycles (use of an app, diary, calendar, or other methods) was obtained from a subsequent questionnaire distributed in December 2021. This questionnaire was returned by 3044 (76.6 %) and 2702 (77.0 %), respectively, of the women in the first and second dose study samples.

2.3. Statistical analyses

The prevalence of menstrual disturbances was calculated before and after first and second vaccine dose, by vaccine type, vaccine combinations, and by dose-interval.

For the main analysis we used a self-controlled case series (SCCS) design [26], in which only vaccinated cases with the outcome in question were included in the data set. The cases were their own control in the sense that we compared the woman's risk of the outcome within a specified exposure window with the risk in a non-exposed window. We used the last menstrual cycle *before* vaccination as the non-exposed window and the first menstrual cycle *after* vaccination as the exposed window. Log-binomial regression was used to estimate risk ratios (RRs) and 95 % confidence intervals (CIs). The model was fitted with generalized estimating equations to account for the within-individual dependencies. Since comparisons are made within individuals, the SCCS method implicitly controls for all fixed confounders. The analyses were performed for any vaccine and by vaccine type, separately for the first and second dose.

In addition, we performed the SCCS analysis stratified by previous gynecological condition and by use of contraception/hormone treatment. We also performed sensitivity analyses in the following subgroups 1) women with no positive laboratory confirmed SARS-CoV 2-test within 6 weeks after receiving the vaccine dose in question, 2) women who reported regular cycles (always or usually) between 24 and 35 days, bleeding duration 4–8 days, and no gynecological conditions, 3) women who received the second vaccine dose at least 8 weeks (56 days) after the first dose (analysis performed for second dose only, since interval between doses cannot affect results on the first dose), 4) women who reported in the subsequent questionnaire from December 2021 (see above) that they had been tracking their menstrual cycle by use of an app, diary, calendar or other methods for at least 1 year.

Finally, we calculated the uptake of the second dose according to reported menstrual disturbances after the first dose.

Data were analysed with Stata/SE 16.0 (StataCorp) software.

3. Results

Among 5765 women answering the questionnaire, 98.3 % were registered with at least one vaccine dose, and 93.6 % with two doses.

Of the 3972 women in the first dose study sample, 2363 (59.5 %) had received Comirnaty as their first vaccine dose and 1417 (35.7 %) had received Spikevax (Table 1). Vaxzevria was only provided to 4.7 %, and only as a first dose. Comirnaty was given as the second dose to 1703 women (42.3 %) and Spikevax to 1804 women (45.4 %). 465 women (11.7 %) had not received a second vaccine dose as of six weeks prior to completing the questionnaire. The median number of days between the first and second dose was 50 days (7 weeks), with interquartile range 43–58 days (6–8 weeks). This was in accordance with the national vaccine recommendations at the time. The interval between doses was less than 4 weeks for 149 women (4.2 %) and less than 5 weeks for 262 women (7.5 %). Only 6.4 % of the women were registered with a laboratory confirmed SARS-CoV-2 infection by November 1st, 2021 (Table 1).

The median interval between first dose and questionnaire fill-in date was 114 days (16 weeks), and 63 days (9 weeks) between the second dose and fill-in date. 57.4 % reported that their cycles typically lasted between 24 and 35 days, and 73.7 % reported always or usually having regular cycles. Approximately 20 % reported one or more previous gynecological conditions, and 59.5 % used contraception or other hormone treatment (Table 1).

3.1. Prevalence of menstrual disturbances

In the last menstrual cycle prior the first vaccine dose, the prevalence of any reported menstrual disturbance was 36.7 %. After the first vaccine dose the prevalence of any reported menstrual disturbance was 38.8 %. The prevalence of heavier bleeding than usual was 7.6 % in the last menstrual cycle prior to the first vaccine dose compared to 13.6 % in the first cycle after the first dose (Table 2). Similarly, the prevalence of heavy bleeding was 8.2 % before and 15.3 % after the second vaccine dose. The corresponding numbers for prolonged bleeding were 9.3 % before and 12.5 % after the first dose, and 8.2 % before and 14.3 % after the second dose (Table 2). The results were similar when stratified by vaccine type (Supplementary Table 1), both for homologous and heterologous regimens (Supplementary Table 2). Finally, we observed similar prevalence of menstrual disturbances before and after the second dose among women with dose-intervals shorter than 56 days and women with dose-intervals of 56 days or longer (Supplementary Table 3).

3.2. Self-controlled case series analyses

We observed increased risk of heavier menstrual bleeding than usual after both the first and second vaccine dose, RR = 1.90 (95 % CI 1.69–2.13) and RR = 1.84 (95 % CI 1.66–2.03), respectively (Table 3). Increased risks after both the first and second dose were also seen for prolonged bleeding (RR = 1.46 (95 % CI 1.31–1.61) for dose 1 and 1.71 (95 % CI 1.55–1.89) for dose 2); shorter interval (RR = 1.32 (95 % CI 1.19–1.46) for dose 1 and 1.57 (95 % CI 1.42–1.73) for dose 2); and stronger period pain (RR = 1.35 (95 % CI 1.24–1.47) for dose 1 and 1.62 (95 % CI 1.49–1.77) for dose 2). For spot bleedings, only a slight increase was seen after the first dose. In general, the RRs of menstrual disturbances were somewhat higher after the second vaccine dose compared with the first. Results were similar for Comirnaty and Spikevax for both doses. Vaxzevria was only used for the first dose and risks were higher

Table 1
Characteristics of COVID-19 vaccinated women from the Young Adult Cohort (Oslo, Norway) included in the first dose study sample, N = 3972.

	n (%)
Year of birth	
1991–1992	817 (20.6)
1993–1994	1128 (28.4)
1995–1996	885 (22.3)
1997–1998	490 (12.3)
1999–2000	306 (7.7)
2001–2003	346 (8.7)
Number of vaccine doses received[1]	
1 dose only[2]	465 (11.7)
2 doses	3507 (88.3)
Vaccine type first dose	
Comirnaty	2362 (59.5)
Spikevax	1417 (35.7)
Vaxzevria	186 (4.7)
Jcovden	6 (0.2)
Vaccine type second dose	
Comirnaty	1703 (42.3)
Spikevax	1804 (45.4)
Vaxzevria	0 (0)
Jcovden	0 (0)
Not received dose 2[2]	465 (11.7)
Laboratory confirmed SARS-CoV-2[3]	
Yes	255 (6.4)
Number of days between menstrual cycles	
≤ 23 days	967 (24.3)
24–35 days	2280 (57.4)
>35 days	505 (12.7)
Missing	220 (5.5)
Normal length of bleeding	
1–3 days	518 (13.0)
4–8 days	3146 (79.2)
≥9 days	102 (2.6)
Missing	206 (5.2)
Regular cycles	
Always regular	810 (20.4)
Usually regular	2118 (53.3)
Usually irregular	517 (13.0)
Always irregular	249 (6.3)
Missing	278 (7.0)
Menstrual tracking[4]	
≥1 year	1174 (29.6)
<1 year	399 (10.0)
Missing/don't know	983 (24.7)
Previous gynaecological conditions[5,6]	
Myoma	
Yes	46 (1.2)
Missing/don't know	112 (2.8)
Endometriosis	
Yes	62 (1.6)
Missing/don't know	154 (3.9)
Polycystic ovary syndrome	
Yes	102 (2.6)
Missing/don't know	132 (3.3)
HPV infection[7]	
Yes	330 (8.3)
Missing/don't know	441 (11.1)
Abnormal cervical cells[7]	
Yes	324 (8.2)
Missing/don't know	435 (11.0)
Cervical cancer[7]	
Yes	3 (0.1)
Missing/don't know	393 (9.9)
Ovarian cyst[7]	
Yes	235 (5.9)
Missing/don't know	451 (11.4)
Other conditions	
Yes	220 (5.5)
Missing/don't know	122 (3.1)
At least 1 reported diagnosis/disease	
Yes	776 (19.5)
Missing/don't know	668 (16.8)
Contraception and/or hormone therapy[5,6]	
Yes	2365 (59.5)
Missing	76 (1.9)
Combination pill	
Yes	1347 (33.9)
Missing	75 (1.9)
Progesterone only pill	
Yes	133 (3.3)
Missing	75 (1.9)
Copper intrauterine device	
Yes	98 (2.5)
Missing	75 (1.9)
Hormonal intrauterine device	
Yes	464 (11.7)
Missing	75 (1.9)
Contraceptive implant	
Yes	256 (6.4)
Missing	75 (1.9)
Other contraception	
Yes	81 (2.0)
Missing	75 (1.9)
Hormone replacement therapy	
Yes	10 (0.3)
Missing	75 (1.9)
Other hormone therapy	
Yes	40 (1.0)
Missing	75 (1.9)

[1] As of 6 weeks prior to completing the questionnaire.
[2] Not included in the second dose study sample. Of these women, 254 women had only received one dose at the time of completing the questionnaire, whereas 211 women had received dose 2, but less than 6 weeks prior to completion of the questionnaire.
[3] Positive test before November 1, 2021.
[4] Information on active tracking of menstrual cycles (app, diary, calendar, other methods) was obtained from a subsequent questionnaire distributed in December 2021, which was completed by 3044 of 3972 women (76.6 %) in the study sample.
[5] Information on gynaecological conditions and contraception/hormone use was obtained from two previous questionnaires distributed in September 2021. These questionnaires were not completed by all women in the study sample.
[6] The number of women categorized as "no" can be found by subtracting the number of women categorized as "yes" and the number of women categorized as "missing/don't know" or "missing" from 3972 (number of women in the entire study sample).
[7] The question on this condition was only included in one of the two previous questionnaires (see footnote 4), and the proportion with missing information may therefore be higher than for some of the other conditions.

for heavier bleeding, but numbers were low and confidence intervals were wide.

Similar patterns, with slightly higher estimates after the second dose, were observed in analyses stratified by previous gynecological conditions. In general, estimates were similar for women reporting and women not reporting previous gynecological conditions (Table 4). Notably, no clear differences across specific conditions were observed (Supplementary Table 4).

Generally, RRs were similar among users and non-users of contraception or other hormone therapy, although estimates for heavier bleeding after the first dose tended to be higher for users of hormonal IUD and copper IUD (Table 5).

In analyses excluding women with a positive laboratory confirmed SARS-CoV 2-test within 6 weeks after receiving dose one or two, the results remained unchanged (results not shown).

When restricting the analyses to women who reported regular menstrual cycles between 24 and 35 days, duration of bleeding 4–8 days and no reported gynecological conditions, risk estimates tended to be somewhat strengthened as compared to the analyses in the full sample (Supplementary Table 5).

Among women with dose-intervals of at least 56 days, results on the second vaccine dose were similar to the main results (Supplementary Table 6).

Of the women in the first and second dose study samples, 1174 (29.6 %) and 1048 (29.9 %) women, respectively, reported in the subsequent questionnaire that they had tracked their menstrual cycles for at least one year. A subgroup analysis among these women showed that the RRs tended to be somewhat higher after the first dose and somewhat lower after the second dose, as compared to the RRs for the total study samples (Supplementary Table 7).

Among women who reported menstrual disturbances after the first dose, 92.5 % were also vaccinated with a second dose, while 94.1 % of those who did not report any disturbances after the first dose, were vaccinated with dose 2 (Supplementary Table 8).

4. Discussion

We assessed and compared the prevalence of several menstrual disturbances before and after COVID-19 vaccination in a cohort of women aged 18–30 years. In the first cycle after vaccination, we observed an increased occurrence of unusually heavy and prolonged bleeding, spot bleeding, interval changes, and increased pain during periods, as compared to the last cycle prior to vaccination. The association with vaccination was strongest for heavy menstrual bleeding increasing from 8 % before vaccination to 14–15 % after vaccination, corresponding to an almost two-fold increased risk. The association between vaccination and menstrual disturbances did not differ according to vaccine type/brand, use of contraception/hormones, or history of gynecological condition(s).

Heavy menstruation was early suspected as a side effect of COVID-19 vaccination due to the spontaneous reporting of such adverse events after COVID-19 vaccination. To date, several post-marketing studies on menstrual disturbances after such vaccination have been conducted.

We have studied the frequency of describing the last menstruation as unusually heavy or prolonged. This can be encountered in women with and without current heavy menstrual bleeding. Although difficult to assess accurately, it has been suggested that the normal cycle-to-cycle variability in menstrual blood loss may be considerable [27]. In a detailed study performed half a century ago, Cole et al. measured the menstrual blood loss in two consecutive cycles in 350 women. The mean blood loss was 37.5 mL, and the difference between two cycles was greater than 20 mL in 18 % of the women. Another study of reproductive aged women found evidence of heavy bleedings with blood loss ≥80 mL among 10 % [28]. In a cohort study of 1500 women, the one-year cumulative incidence of experiencing period(s) heavier than usual was 21 % (16 % in women less than 35 years, and 23–24 % in women ≥35 years) [29], in line with other studies based on self-reports [30,31]. Unusually heavy menstruation will therefore inevitably be prevalent also in post-vaccination cycles. The observed prevalence of heavy menstrual bleeding after COVID-19 vaccination was much higher in a study by Lee et al. than in our study, 42 % and 14–15 %, respectively [4]. Due to recruitment through social media, there may have been a selection of participants that had noticed menstrual changes in this study, and as acknowledged by the authors, their results may be biased.

Several previous studies have compared risk of heavy menstrual bleeding after COVID-19 vaccination to risk among unvaccinated and/or pre-vaccination, but results are conflicting [19,20,22,32,33]. In a study analyzing flow characteristics among 9500 women using the "Natural Cycles" application, vaccinated individuals more often experienced increased bleeding quantity as compared to unvaccinated individuals [19]. However, while the association between vaccination and flow changes was weak, such changes were very common in both vaccinated and unvaccinated individuals (38.4 % and 34.5 %, respectively). Only participants with complete data on menstrual quantity were eligible for inclusion in the study. It is possible that these women had particular reasons for detailed tracking of their cycle, which could be a potential reason for the high prevalence of flow changes. A Swedish nationwide register-based study of hospital visits for menstrual disturbances among women aged 12–49 years observed very weak associations in the main risk window, defined as 8–90 days within receipt of COVID-19 vaccine; HR was 1.07 (95 % CI 1.00–1.14) after dose 1, 1.04 (95 % CI 0.98–1.10) after dose 2, and 1.00 (95 % CI 0.89–1.13) after dose 3 [33]. However, a 26 % increased risk was observed 1–7 days within dose 1, HR 1.26 (95 % CI 1.11–1.42). Notably, the outcome in this study included both absent, scant, or rare menstruation (ICD-10 code N.91) and excessive, frequent, and irregular menstruation (ICD-10 code N.92). Flow-changes after vaccination were not detected in a small prospective cohort [20], nor in another application-based study [22]. In contrast, a previous study from the Norwegian Institute of Public Health based on a separate cohort, found that vaccination was associated with a 1.6-fold increased risk of heavier bleeding in adolescent girls (12–15 years) [32]. The reason for these conflicting results is not known.

We did not detect differences in the association between vaccination and menstrual disturbances according to vaccine type/brand, contraception/hormone use, nor to the presence of gynecological condition(s). To date, few studies exist for comparison and the results only partially agree. Consistent with our finding, vaccine type/brand did not affect the risk of heavy bleeding in two other studies [4,19]. While PCOS was associated with lighter flow, other gynecological conditions did not affect the risk of flow changes in a retrospectively recruited cohort [20]. Gynecological conditions were associated with more frequent reporting of heavy bleeding in a large cross-sectional survey [4]. Hormonal contraception users were slightly more prone to report changes in flow as compared to women with natural cycles in both latter studies [4,20], but were less likely to report changes in another study [21]. It is possible that smaller risk differences according to these factors may have gone undetected in our study due to power limitations. However, it seems probable that the risk of heavy menstruation after vaccination is also generally increased, irrespective of these factors.

In analyses restricted to women who reported to always or usually have regular, normal length menstruations and no reported gynecological conditions, results were similar to the main results, indicating that the association was not explained by women usually having irregular menstruation.

A growing body of evidence suggests that COVID-19 vaccination is associated with an average increase in cycle lengths [17,18,22], especially if the woman is vaccinated during the follicular phase [18,22]. We detected an increased risk of longer interval after the second dose, but also an increased risk of *shorter* interval after vaccination. Unfortunately, we did not have information on the change in days and could therefore not assess the mean change, as previous studies have done. However, when interpreting mean changes in cycle length, it must be kept in mind, that a small mean change could be a result of greater changes in both directions (i.e. both shorter and longer interval). Of note, it has been suggested that cycle changes may result from pandemic-related stress, rather than vaccination. However, a large cohort study based on application-data did not find population level cycle changes during the pandemic [34].

Results from previous studies suggest that menstrual disturbances after vaccination are mostly short lived [17,19]. The average increase in the post-vaccination cycle length reported by Edelman et al. nearly normalized in the consecutive cycle [17]. The average 4 % increase in total bleeding quantity after COVID-19 vaccination observed in users of the "Natural Cycles" application [19], was

Table 2
Number and prevalence of menstrual disturbances before and after COVID-19 vaccination among women in the Young Adult Cohort (Oslo, Norway), for the first dose (N = 3972) and second dose (N = 3507).

	Last cycle prior to dose 1, n (%)	First cycle after dose 1, n (%)	Last cycle prior to dose 2, n (%)	First cycle after dose 2, n (%)
Heavier bleeding[1]				
Yes	301 (7.6)	541 (13.6)	287 (8.2)	538 (15.3)
Don't know	182 (4.6)	236 (5.9)	207 (5.9)	187 (5.3)
Missing[2]	33 (0.8)	42 (1.1)	38 (1.1)	51 (1.5)
Prolonged bleeding[1]				
Yes	368 (9.3)	498 (12.5)	289 (8.2)	503 (14.3)
Don't know	154 (3.9)	211 (5.3)	192 (5.5)	185 (5.3)
Missing[2]	34 (0.9)	36 (0.9)	38 (1.1)	50 (1.4)
Shorter interval[1]				
Yes	376 (9.5)	478 (12.0)	278 (7.9)	449 (12.8)
Don't know	203 (5.1)	229 (5.8)	219 (6.2)	212 (6.0)
Missing[2]	43 (1.1)	45 (1.1)	41 (1.2)	48 (1.4)
Longer interval[1]				
Yes	411 (10.3)	432 (10.9)	294 (8.4)	369 (10.5)
Don't know	228 (5.7)	233 (5.9)	204 (5.8)	208 (5.9)
Missing[2]	37 (0.9)	41 (1.0)	41 (1.2)	47 (1.3)
Spot bleeding[1]				
Yes	549 (13.8)	563 (14.2)	350 (10.0)	529 (15.1)
Don't know	146 (3.7)	188 (4.7)	177 (5.0)	171 (4.9)
Missing[2]	34 (0.9)	40 (1.0)	41 (1.2)	45 (1.3)
Stronger period pains[1]				
Yes	451 (11.4)	579 (14.6)	343 (9.8)	561 (16.0)
Don't know	166 (4.2)	214 (5.4)	196 (5.6)	196 (5.6)
Missing[2]	32 (0.8)	44 (1.1)	41 (1.2)	51 (1.5)
Period pains without bleeding[1]				
Yes	725 (18.3)	627 (15.8)	411 (11.8)	579 (16.5)
Don't know	153 (3.9)	212 (5.3)	193 (5.5)	180 (5.1)
Missing[2]	38 (1.0)	33 (0.8)	44 (1.3)	51 (1.5)
Any menstrual disturbance				
Yes	1457 (36.7)	1540 (38.8)	991 (28.3)	1408 (40.1)
Don't know/missing	297 (7.5)	324 (8.2)	304 (8.7)	284 (8.1)

[1] The participants could respond either "yes", "no", or "don't know" to the questions on menstrual disturbances before/after vaccine dose 1 and before/after vaccine dose 2.
[2] The relevant question was not answered.

reduced (2.8 %) in the consecutive cycle. Our study was not based on tracking of consecutive cycles, and duration of the menstrual disturbances was not measured. The first and second doses were administered with a median interval of 7 weeks, suggesting that most participants had no more than two menstrual bleedings between their doses. The prevalence of heavy menstrual bleeding was only slightly higher in the last cycle before the second dose (8.2 %) as compared to the last cycle before the first dose (7.6 %), and for the other outcomes the prevalence was slightly lower before the second dose. This could indicate that for most women, the change lasted for only one cycle and that the menstruation normalized between doses. The Swedish nation-wide study of health care contacts for abnormal menstrual bleeding found little evidence of increased risk after COVID-19 vaccination among women aged 12–49 years [33]. A possible explanation for the weak association in their study could be that menstrual changes after vaccination are generally short-lived and of a non-serious character, and thus unlikely to result in women seeking health care.

The present study has several limitations that need to be addressed. Most importantly, recall bias is a concern. The outcomes in this study are self-reported and retrospectively collected at a single time point. The current questionnaire was administered in October 2021, when most women were vaccinated twice, and the media attention was significant. Thus, there is a possibility for overestimation of the association between vaccination and menstrual disturbances, if women were more prone to notice, recall or report events after vaccination. Since menstrual disturbances are common, accurate recall is challenging, especially considering the potentially long time between the outcome and completion of the questionnaire. The prevalence of many outcomes was slightly higher before dose 1 than before dose 2, and 36.7 % vs 28.3 % for at least one reported menstrual disturbance. This was somewhat unexpected, since any potential changes after the first dose lasting more than one or two cycles, should have resulted in a higher prevalence before the second dose. Recall is likely to be more inaccurate for menstrual characteristics further back in time (i.e., before the first dose). Possibly, menstrual disturbances before the first dose may have been overreported since it might be difficult to recall whether a disturbance occurred in the last cycle before the first vaccine dose or a previous cycle. Precise dating of a menstrual bleeding may improve the recollection of any abnormalities related to that bleeding, as well as being confirmative of the temporal sequence of vaccination and a given cycle. Reassuringly, estimates based on women who reported tracking their periods with an application or other methods, were similar to the main results.

Furthermore, we lack information on timing of menstruation. Thus, where in the menstrual cycle the participants were vaccinated and the number of menstrual cycles between vaccine doses cannot be ascertained. 7.5 % of the women in this study received the second vaccine dose less than 5 weeks after the first. Thus, some women have only had one menstrual bleeding between the vaccine doses, and consequently the first menstrual bleeding after the first dose was the same as the last menstrual bleeding before the second dose. These women would falsely be considered unexposed to vaccination in their last menstrual bleeding before the second dose. Provided that vaccination increases menstrual disturbances, such misclassification would result in prevalences before the second dose that are higher than what would be observed among unvaccinated women. However, the prevalence of each outcome was quite similar before the first and second vaccine doses. Moreover, the RRs observed in a subgroup of women who received the second vaccine dose at least 8 weeks after the first dose, were quite similar to those observed in the entire study sample. Since

Table 3
Self-controlled case series analysis of COVID-19 vaccination and menstrual disturbances among women in the Young Adult Cohort (Oslo, Norway), by dose and vaccine type.

	Number of cases			Risk Ratio (95 % CI)
	Total[1]	Prior to vaccination	After vaccination	
Heavier bleeding				
Dose 1				
Any vaccine[2]	634	273	518	1.90 (1.69–2.13)
Comirnaty	387	168	317	1.89 (1.63–2.18)
Spikevax	218	95	177	1.86 (1.54–2.26)
Vaxzevria	29	10	24	2.40 (1.29–4.46)
Dose 2				
Any vaccine	557	270	496	1.84 (1.66–2.03)
Comirnaty	269	134	235	1.75 (1.52–2.02)
Spikevax	286	135	259	1.92 (1.67–2.21)
Prolonged bleeding				
Dose 1				
Any vaccine[2]	636	335	488	1.46 (1.31–1.61)
Comirnaty	363	187	283	1.51 (1.32–1.73)
Spikevax	241	129	186	1.44 (1.22–1.70)
Vaxzevria	31	18	19	1.06 (0.62–1.79)
Dose 2				
Any vaccine	541	274	469	1.71 (1.55–1.89)
Comirnaty	255	136	224	1.65 (1.44–1.89)
Spikevax	286	138	245	1.78 (1.53–2.06)
Shorter interval				
Dose 1				
Any vaccine[2]	603	346	456	1.32 (1.19–1.46)
Comirnaty	353	206	268	1.31 (1.15–1.48)
Spikevax	218	125	165	1.32 (1.12–1.56)
Vaxzevria	31	15	23	1.53 (0.91–2.57)
Dose 2				
Any vaccine	488	269	421	1.57 (1.42–1.73)
Comirnaty	238	134	196	1.46 (1.26–1.69)
Spikevax	250	135	225	1.67 (1.46–1.90)
Longer interval				
Dose 1				
Any vaccine[2]	594	389	415	1.07 (0.97–1.17)
Comirnaty	370	243	267	1.10 (0.98–1.23)
Spikevax	199	132	133	1.01 (0.85–1.19)
Vaxzevria	23	13	14	1.08 (0.57–2.03)
Dose 2				
Any vaccine	434	278	346	1.24 (1.13–1.37)
Comirnaty	211	134	164	1.22 (1.06–1.42)
Spikevax	223	144	182	1.26 (1.11–1.44)
Spot bleeding				
Dose 1				
Any vaccine[2]	725	502	547	1.09 (1.01–1.17)
Comirnaty	421	286	324	1.13 (1.02–1.25)
Spikevax	265	193	194	1.01 (0.89–1.13)
Vaxzevria	38	22	29	1.32 (0.89–1.94)
Dose 2				
Any vaccine	559	330	492	1.49 (1.37–1.62)
Comirnaty	271	161	236	1.47 (1.30–1.65)
Spikevax	288	166	256	1.51 (1.35–1.70)
Stronger period pains				
Dose 1				
Any vaccine	706	417	563	1.35 (1.24–1.47)
Comirnaty	437	262	345	1.32 (1.18–1.46)
Spikevax	237	134	194	1.45 (1.25–1.68)
Vaxzevria	32	21	24	1.14 (0.78–1.67)
Dose 2				
Any vaccine	582	321	521	1.62 (1.49–1.77)
Comirnaty	277	162	243	1.50 (1.33–1.69)
Spikevax	305	159	278	1.75 (1.55–1.98)
Period pains without bleeding				
Dose 1				
Any vaccine	830	667	608	0.91 (0.86–0.97)
Comirnaty	492	397	367	0.92 (0.86–1.00)
Spikevax	296	235	214	0.91 (0.82–1.01)
Vaxzevria	42	35	27	0.77 (0.57–1.04)

(*continued on next page*)

Table 3 (*continued*)

	Number of cases			Risk Ratio (95 % CI)
	Total[1]	Prior to vaccination	After vaccination	
Dose 2				
Any vaccine	583	388	527	1.36 (1.27–1.45)
Comirnaty	281	188	251	1.34 (1.21–1.48)
Spikevax	302	200	276	1.38 (1.26–1.52)

[1] Number of women included in each analysis. All women included in each analysis reported that they had experienced the relevant menstrual disturbance either before vaccination, after vaccination, or both. Women who answered «don't know» or did not answer the question about the relevant menstrual disturbance before and/or after vaccination were excluded. Thus, the number of cases does not correspond exactly to the number of cases presented in Table 2.

[2] The number of cases reported after "any vaccine" may be higher than the sum of cases reported for Comirnaty, Spikevax and Vaxzevria because some of the cases may have been reported after other vaccine types.

Table 4
Self-controlled case series analysis of COVID-19 vaccination and menstrual disturbances among women in the Young Adult Cohort (Oslo, Norway), by dose and report of previous gynecological condition.

	Number of cases			Risk Ratio (95 % CI)
	Total[1]	Prior to vaccination	After vaccination	
Heavier bleeding				
Dose 1				
No previous gynecological condition	361	144	294	2.04 (1.74–2.40)
Previous gynecological condition	146	73	115	1.58 (1.27–1.99)
Dose 2				
No previous gynecological condition	325	159	289	1.82 (1.60–2.07)
Previous gynecological condition	126	59	108	1.83 (1.46–2.30)
Prolonged bleeding				
Dose 1				
No previous gynecological condition	348	181	270	1.49 (1.30–1.71)
Previous gynecological condition	154	87	109	1.25 (1.01–1.55)
Dose 2				
No previous gynecological condition	313	155	270	1.74 (1.52–2.00)
Previous gynecological condition	118	52	102	1.96 (1.54–2.50)
Shorter interval				
Dose 1				
No previous gynecological condition	352	194	271	1.40 (1.22–1.59)
Previous gynecological condition	137	81	99	1.22 (0.99–1.51)
Dose 2				
No previous gynecological condition	560	160	237	1.48 (1.30–1.69)
Previous gynecological condition	240	58	101	1.74 (1.38–2.19)
Long interval				
Dose 1				
No previous gynecological condition	698	230	242	1.05 (0.93–1.19)
Previous gynecological condition	264	84	95	1.13 (0.92–1.38)
Dose 2				
No previous gynecological condition	254	162	207	1.28 (1.13–1.45)
Previous gynecological condition	92	55	70	1.27 (1.00–1.62)
Spot bleeding				
Dose 1				
No previous gynecological condition	412	285	306	1.07 (0.97–1.19)
Previous gynecological condition	183	126	140	1.11 (0.96–1.29)
Dose 2				
No previous gynecological condition	316	188	273	1.45 (1.30–1.62)
Previous gynecological condition	150	80	134	1.68 (1.41–2.00)
Stronger period pains				
Dose 1				
No previous gynecological condition	391	217	308	1.42 (1.26–1.60)
Previous gynecological condition	164	104	130	1.25 (1.06–1.47)
Dose 2				
No previous gynecological condition	330	167	302	1.81 (1.60–2.04)
Previous gynecological condition	142	85	122	1.43 (1.21–1.70)
Period pains without bleeding				
Dose 1				
No previous gynecological condition	470	380	333	0.88 (0.81–0.95)
Previous gynecological condition	192	156	141	0.90 (0.80–1.02)
Dose 2				
No previous gynecological condition	321	210	291	1.39 (1.26–1.52)
Previous gynecological condition	150	99	137	1.38 (1.21–1.58)

[1] Number of women included in each analysis. All women included in each analysis reported that they had experienced the relevant menstrual disturbance either before vaccination, after vaccination, or both. Women who answered «don't know» or did not answer the question about the relevant menstrual disturbance before and/or after vaccination were excluded. Women with missing information on previous gynecological conditions were also excluded.

Table 5
Self-controlled case-series analysis of COVID-19 vaccination and menstrual disturbances among women in the Young Adult Cohort (Oslo, Norway), by dose and use of contraception/hormones.

	Number of cases			Risk Ratio (95 % CI)
	Total[1]	Prior to vaccination	After vaccination	
Heavier bleeding				
Dose 1				
Contraception or hormone therapy, No	271	113	225	1.99 (1.67–2.37)
Contraception or hormone therapy[2], Yes	345	154	278	1.81 (1.55–2.10)
Combination pill	175	82	131	1.60 (1.28–1.99)
Progesteron only pill	27	14	24	1.71 (1.12–2.63)
Contraceptive implant	51	23	42	1.83 (1.24–2.68)
Hormonal intrauterine device	66	28	59	2.11 (1.52–2.91)
Copper intrauterine device	22	8	18	2.25 (1.12–4.50)
Dose 2				
Contraception or hormone therapy, No	225	118	201	1.70 (1.47–1.98)
Contraception or hormone therapy[2], Yes	322	147	285	1.94 (1.69–2.23)
Combination pill	134	64	119	1.86 (1.51–2.29)
Progesteron only pill	23	9	19	2.11 (1.12–3.99)
Contraceptive implant	60	28	57	2.04 (1.52–2.72)
Hormonal intrauterine device	66	28	55	1.96 (1.38–2.79)
Copper intrauterine device	26	12	25	2.08 (1.34–3.23)
Prolonged bleeding				
Dose 1				
Contraception or hormone therapy, No	195	93	147	1.58 (1.29–1.94)
Contraception or hormone therapy[2], Yes	423	231	326	1.41 (1.25–1.59)
Combination pill	168	86	120	1.40 (1.12–1.74)
Progesteron only pill	35	22	27	1.23 (0.85–1.77)
Contraceptive implant	89	52	72	1.38 (1.09–1.75)
Hormonal intrauterine device	108	62	89	1.44 (1.16–1.78)
Copper intrauterine device	18	9	12	1.33 (0.64–2.77)
Dose 2				
Contraception or hormone therapy, No	163	83	140	1.69 (1.40–2.03)
Contraception or hormone therapy[2], Yes	364	180	317	1.76 (1.55–2.00)
Combination pill	130	58	114	1.97 (1.57–2.46)
Progesteron only pill	28	12	24	1.85 (1.14–2.99)
Contraceptive implant	68	41	63	1.54 (1.24–1.91)
Hormonal intrauterine device	109	53	90	1.70 (1.32–2.17)
Copper intrauterine device	22	10	20	2.00 (1.19–3.36)
Shorter interval				
Dose 1				
Contraception or hormone therapy, No	203	113	145	1.28 (1.07–1.54)
Contraception or hormone therapy[2], Yes	382	222	296	1.33 (1.18–1.50)
Combination pill	129	73	97	1.33 (1.07–1.65)
Progesteron only pill	36	23	28	1.22 (0.85–1.73)
Contraceptive implant	91	61	68	1.11 (0.89–1.39)
Hormonal intrauterine device	114	59	95	1.61 (1.29–2.02)
Copper intrauterine device	16	9	11	1.22 (0.62–2.42)
Dose 2				
Contraception or hormone therapy, No	160	89	133	1.49 (1.25–1.79)
Contraception or hormone therapy[2], Yes	319	174	279	1.60 (1.42–1.81)
Combination pill	109	50	101	2.02 (1.61–2.53)
Progesteron only pill	32	17	27	1.59 (1.05–2.39)
Contraceptive implant	68	41	62	1.51 (1.21–1.89)
Hormonal intrauterine device	92	59	74	1.25 (1.01–1.55)
Copper intrauterine device	15	8	12	1.50 (0.80–2.82)
Longer interval				
Dose 1				
Contraception or hormone therapy, No	311	189	231	1.22 (1.07–1.40)
Contraception or hormone therapy[2], Yes	266	189	173	0.92 (0.79–1.05)
Combination pill	68	44	47	1.07 (0.80–1.43)
Progesteron only pill	23	17	18	1.06 (0.73–1.54)
Contraceptive implant	64	51	36	0.71 (0.53–0.95)
Hormonal intrauterine device	87	60	58	0.97 (0.75–1.24)
Copper intrauterine device	19	11	12	1.09 (0.56–2.11)
Dose 2				
Contraception or hormone therapy, No	228	142	184	1.30 (1.13–1.49)
Contraception or hormone therapy[2], Yes	194	126	153	1.21 (1.05–1.41)
Combination pill	50	34	40	1.18 (0.90–1.54)
Progesteron only pill	22	16	17	1.06 (0.72–1.58)
Contraceptive implant	45	28	34	1.21 (0.87–1.70)
Hormonal intrauterine device	62	41	47	1.15 (0.88–1.50)
Copper intrauterine device	10	4	10	–[3]
Spot bleeding				
Dose 1				
Contraception or hormone therapy, No	151	91	106	1.16 (0.95–1.43)
Contraception or hormone therapy[2], Yes	552	396	423	1.07 (0.99–1.16)

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Table 5 (*continued*)

	Number of cases			Risk Ratio (95 % CI)
	Total[1]	Prior to vaccination	After vaccination	
Combination pill	264	185	198	1.07 (0.95–1.21)
Progesteron only pill	48	35	40	1.14 (0.90–1.45)
Contraceptive implant	93	76	70	0.92 (0.78–1.09)
Hormonal intrauterine device	130	90	101	1.12 (0.95–1.33)
Copper intrauterine device	18	11	15	1.36 (0.84–2.21)
Dose 2				
Contraception or hormone therapy, No	116	68	100	1.47 (1.22–1.78)
Contraception or hormone therapy[2], Yes	431	252	380	1.51 (1.37–1.66)
Combination pill	199	108	178	1.65 (1.42–1.91)
Progesteron only pill	31	18	27	1.50 (1.04–2.16)
Contraceptive implant	66	40	61	1.53 (1.22–1.90)
Hormonal intrauterine device	111	74	95	1.28 (1.08–1.52)
Copper intrauterine device	17	11	13	1.18 (0.70–1.98)
Stronger period pains				
Dose 1				
Contraception or hormone therapy, No	311	185	246	1.33 (1.17–1.51)
Contraception or hormone therapy[2], Yes	374	215	298	1.39 (1.23–1.56)
Combination pill	173	97	135	1.39 (1.16–1.67)
Progesteron only pill	20	12	15	1.25 (0.74–2.12)
Contraceptive implant	48	28	36	1.29 (0.91–1.82)
Hormonal intrauterine device	112	70	92	1.31 (1.08–1.59)
Copper intrauterine device	16	7	14	2.00 (1.04–3.86)
Other contraception	9	5	9	–[3]
Dose 2				
Contraception or hormone therapy, No	248	146	217	1.49 (1.31–1.69)
Contraception or hormone therapy[2], Yes	323	166	293	1.77 (1.56–1.99)
Combination pill	141	71	132	1.86 (1.55–2.23)
Progesteron only pill	16	6	14	2.33 (1.11–4.89)
Contraceptive implant	47	23	43	1.87 (1.34–2.60)
Hormonal intrauterine device	96	57	81	1.42 (1.15–1.76)
Copper intrauterine device	16	6	15	2.50 (1.26–4.96)
Other contraception	11	6	11	–[3]
Period pain without bleeding				
Dose 1				
Contraception or hormone therapy, No	300	241	220	0.91 (0.83–1.01)
Contraception or hormone therapy[2], Yes	501	403	365	0.91 (0.84–0.98)
Combination pill	199	155	134	0.86 (0.75–1.00)
Progesteron only pill	26	19	20	1.05 (0.73–1.51)
Contraceptive implant	70	51	54	1.06 (0.85–1.32)
Hormonal intrauterine device	179	158	137	0.87 (0.78–0.96)
Copper intrauterine device	24	17	20	1.18 (0.83–1.67)
Other contraception	12	11	9	0.82 (0.55–1.21)
Dose 2				
Contraception or hormone therapy, No	197	132	176	1.33 (1.18–1.50)
Contraception or hormone therapy[2], Yes	374	245	340	1.39 (1.27–1.51)
Combination pill	151	92	140	1.52 (1.32–1.76)
Progesteron only pill	17	13	11	0.85 (0.50–1.42)
Contraceptive implant	47	31	46	1.48 (1.20–1.84)
Hormonal intrauterine device	133	96	120	1.25 (1.10–1.42)
Copper intrauterine device	19	10	17	1.70 (1.03–2.80)
Other contraception	11	5	11	–[3]

[1] Number of women included in each analysis. All women included in each analysis reported that they had experienced the relevant menstrual disturbance either before vaccination, after vaccination, or both. Women who answered «don't know» or did not answer the question about the relevant menstrual disturbance before and/or after vaccination were excluded. Women with missing information on use of contraception/hormone therapy were also excluded.

[2] Information on type of contraception was missing for some women who reported using contraception or hormone treatment, thus this number may be higher than the sum of different treatments listed below.

[3] Analysis not performed due to insufficient number of cases.

the women in this subgroup were unlikely to have had only one menstrual bleeding between vaccine doses, this may indicate that the misclassification did not lead to biased results.

An assumption in the SCCS model is that the probability of being vaccinated is not affected by the occurrence of menstrual disturbances [35]. Although heavy menstrual bleeding has only recently been acknowledged as a potential side effect, early anecdotal reports could potentially have given rise to vaccine hesitancy or refusal in women with such complaints before vaccination. However, the similar vaccine coverage for the second dose among those with and without reported disturbances after the first dose (92.5 % and 94.1 %, respectively) is reassuring. The self-controlled design accounts for individual characteristics and risk factors that are constant over the study period. Linkage to the Norwegian Immunisation Registry ensured a precise and objective measure of vaccination status. Both men and women were invited to participate in the cohort, and questions about menstrual disturbances were unannounced. There may be a selection of health-conscious and well-educated women in the cohort, particularly since the participants were recruited from a city. However, the broad aim of the cohort as well as the consistently high response rate to the cohort questionnaires, suggests a low risk of a biased sample with respect to menstrual disturbances. The vaccine coverage in the cohort was comparable to the general population.

5. Conclusions

The detection of an increased risk of heavy menstrual bleeding and other menstrual disturbances after COVID-19 vaccination in a sample of young women from the general population of Oslo, supports the initial safety signals from spontaneous reporting systems. Although overestimation due to recall bias and awareness is a concern, the similar results among those actively tracking their menstrual cycles are reassuring. In this cohort, the vaccine uptake for the second dose was high also for women who had reported menstrual disturbances after the first dose, implying that the menstrual disturbance did not influence willingness to accept a second dose. Whether this is true for other populations, and if the willingness to receive further doses is affected in women with these experiences, is not known. In the future, menstrual characteristics should be routinely included in vaccine trials [36]. Potential mechanisms for the observed disturbances should be explored.

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Data availability

Data protection rules restrict us form sharing the individual level data used in the current study. For questions about data access, researchers may contact the corresponding author.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.06.088.

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