

Increased occurrence of menstrual disturbances in 18- to 30-year-old women after COVID-19 vaccination

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Summary

Background Many signals of menstrual disturbances as possible side effects of vaccination against COVID-19 have been reported. Our objective was to estimate the association between vaccination and the occurrence of such disturbances among women aged 18-30 in Norway.

Methods We used mobile-phone questionnaires to collect reports of menstrual disturbances from 5688 women aged 18-30 years, participating in the population-based Norwegian Young Adult Cohort. We estimated the relative risk of menstrual disturbances according to vaccination in a self-controlled case-series design, using the first six weeks after vaccination as the exposed period. We examined the occurrence of such disorders before and after both the first and second doses of vaccine. For subjects who had a menstrual disturbance after the first dose, we calculated the risk of recurrence after the second dose.

Findings The prevalence of any menstrual disturbance was 37.8% prior to vaccination. The relative risk of more heavy bleeding than usual during the exposed compared to unexposed period for first dose vaccination was 1.90 (95% CI: 1.69-2.13), while it was 1.84 (1.66-2.03) for the second dose. The proportion with menstrual disturbances in the most recent menstruation prior to the second vaccine dose was roughly the same as before the first vaccine dose. The risk of heavy bleeding after the second dose, given that it had occurred after the first, was 65.7%. We observed increased risks after vaccination also for other menstrual disturbances.

Interpretation Menstrual disturbances were generally common regardless of vaccination. We found a significant increase in menstrual disturbances after vaccination, particularly for heavier bleeding than usual, longer duration and for short interval between menstruations. Mechanisms underlying these findings may involve bleeding disturbances in general, as well as endocrine alterations.

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Research in context

Evidence before this study

Vaccination is a central public action to reduce COVID-19 related severe disease and deaths during the current SARS-CoV-2 pandemic. However, a well-functioning surveillance system to detect signs of adverse effects is also paramount. Many reports to government agencies, such as the British Yellow Card Scheme, have concerned menstrual disturbances after COVID-19 vaccination. However, it has proved difficult to estimate the association to vaccination since such disturbances are common among unvaccinated women.

Added value of this study

We established a cohort, the Norwegian Young Adult Cohort, in the spring of 2021 to analyse the uptake, effects and potential adverse effects of COVID-19 vaccination in a population-based sample of subjects aged 18-30 years. This enabled the investigation of menstrual disturbances both before and after vaccination. We report a clear increase in menstrual disturbances after vaccination. The large majority had received mRNA vaccines.

Implications of all the available evidence

We find that menstrual disturbances are more common after COVID-19 vaccination, corroborating reports to government agencies. Further randomised, controlled studies of mRNA vaccines should explicitly ask for menstrual disturbances before and after vaccination. The high recurrence for women who experienced heavy bleeding after the first dose, is relevant information in advisory situations. These associations may stimulate basic molecular research into mechanisms.

Introduction

COVID-19 vaccines are used to curb the COVID-19 pandemic. Unfortunately, questions about menstruation have been excluded from most large-scale COVID-19 vaccine studies. From June 2021 onwards, the Norwegian Medicines Agency received a substantial number of reports of menstrual disturbances through their routine surveillance system for adverse effects of medications and vaccines.¹ The reports consisted mainly of more heavy menstrual bleeding than expected, but also shortened or prolonged intervals between menstruations. In a statement issued in August 2021, the pharmacovigilance assessment committee (PRAC) of the European Medicines Agency (EMA) said that no causal association between COVID-19 vaccines and menstrual disorders had been established so far.²

By September 2021, more than 30 000 reports of menstrual irregularities after vaccination had been reported to the British Yellow Card surveillance system,³ leading to a call for investigations.⁴ However, menstrual irregularities are common. Routine surveillance systems do not include the occurrence of events among non-vaccinated subjects, making it difficult to assess to which extent the reported occurrence of such irregularities are above expected levels.⁴

Prompted by the reports, we have included questions on menstrual disturbances into an ongoing population-based cohort of young adults, where the large majority, more than 90%, had been vaccinated already. Our design was to compare the occurrence of menstrual disturbances before and after vaccination for the same women, with the aim of estimating the association between such irregularities and COVID-19 vaccines.

Methods

Study population

The Young Adult Cohort consists of 12623 subjects (8576 women and 4281 men), aged 18 to 30 years. In all, 97308 subjects, living in the Oslo area, were randomly drawn from the National Population Registry, and invited for participation. The aim of the cohort is to study the consequences of the coronavirus pandemic, including effects of infection, vaccination and other actions. The present sample consists of 5756 female responders to an electronic questionnaire sent out in late October 2021, after most of the participants had received two doses of COVID-19 vaccines. The response rate was 68.4%. The dates of vaccination and types of vaccine used were obtained through a linkage to the National Immunisation Registry (SYSVAK),⁵ using the national personal identification number. We excluded 27 subjects with inconsistency between self-reported vaccination and registry information, and 41 subjects who had received three vaccine doses, leaving 5688 women for analysis.

Variables

The women were first asked about vaccination and if they were having menstruations. Vaccinated, menstruating women were asked whether they had experienced any of the following disturbances in their last menstruation before the first vaccine dose: 1) more heavy bleeding than usual, 2) longer lasting menstruation, 3) shorter interval between menstruations, 4) longer interval between menstruations, 4) spot bleedings between menstruations, 5) stronger pain during menstruation, 6) period pain without bleeding, and 7) any other symptom from the pelvic region. Subsequently, they were asked the same list of questions 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. The average interval between the first and second vaccine dose was 53 days. For some women, only one menstrual bleeding occurred between vaccinations.

Statistical Analyses

We calculated the prevalence of unusual menstrual symptoms before and after vaccine dose one and two respectively. For the main analysis, we used a self-controlled case series (SCCS) design,⁶ 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. The date of vaccination for each individual woman was obtained from the records in SYSVAK. We decided to use the first six weeks after the date of vaccination as the window of exposure, allowing long intermenstrual intervals to occur, and the last menstrual cycle before vaccination as the non-exposed window.

Results

The proportion of women who were vaccinated was high, 91.6% had received two doses (Table 1). About 71% were menstruating, and 59.1% used hormonal contraception or treatment.

Prevalence of menstrual disturbances

Table 2 shows that the prevalence of more heavy bleeding during menstruation was 7.6% in the last menstrual cycle prior to the first vaccine dose compared to 13.6% in the first cycle after vaccination. Similarly, Table 3 shows that the prevalence of heavy bleeding was 8.2% before and 15.3% after the second vaccine dose.

Relative risks

To estimate relative risks, we restricted the sample to include only women who were vaccinated and had experienced a menstrual disturbance, using a self-controlled case series design. We estimated the relative risk of more heavy menstrual bleeding than usual after the first vaccine dose to 1.90 (95% CI 1.69-2.13), and to 1.84 (1.66-2.03) after the second vaccine dose (Table 4). In general, the relative risks of menstrual disturbances were somewhat higher after the second vaccine dose compared with the first (Table 4).

Continuation of vaccination

Among women who reported menstrual disturbances after the first dose, 92.3 per cent were also vaccinated with dose 2. Among women who did not report any disturbances after the first dose, 94 per cent were vaccinated with dose 2.

Recurrence risk

Women who had experienced more heavy bleeding than usual after the first vaccine dose had a high risk of having the same experience after the second vaccine dose, 63.4% (278 out of 423 women). The recurrence risks were of the same magnitude for the other menstrual disturbances.

Discussion

Main conclusions

We calculated the prevalence and relative risk of several menstrual disturbances according to COVID-19 vaccination in a cohort of more than 4000 menstruating women aged 18-30 years. Menstrual disturbances were generally common, with a prevalence close to 40 per cent, regardless of vaccination. Yet, the prevalence of unusually heavy bleeding was higher after the first vaccine dose (13.6 per cent) compared to prior vaccination (7.6 per cent). A similar pattern was observed before and after the first vaccine dose for prolonged bleeding, short intermenstrual interval and increased pain during periods.

On average, menstrual disturbances after the first dose returned to normal by the time the second vaccination was given, approximately two months after the first dose, suggesting that in most cases the menstrual disturbances associated with the first vaccination were transient. The vaccine uptake for the second dose was high also for women who had reported more heavy bleeding than usual after the first dose, implying that the menstrual disturbance did not influence willingness to accept a second dose. The prevalence of menstrual disturbances after dose two was slightly higher than after dose one.

Among women who experienced disturbances after the first dose, almost two out of three women also experienced them after the second dose. Menstrual disturbances after the second dose in women with no disturbances after the first dose was the same as the background prevalence, approximately 8 per cent.

Comparison with other studies

Menstrual disturbances are common.⁷ In order to assess any excess risk caused by COVID-19 vaccines, information on the prevalence of menstrual disturbances in both unvaccinated and vaccinated women are warranted. So far, such studies on the association between vaccination against COVID-19 and menstrual bleedings are lacking. While conducting this study, we searched PubMed and Europe PMC for articles published between July and the end of 2021, using search terms describing "COVID-19 vaccine* and menstrua*" with no language restrictions. Only a few studies were identified.

In a UK survey including almost 5000 vaccinated women,⁸ menstrual disturbance was reported by 20% of individuals up to four months post-vaccination, whereas in our study, almost four out of ten reported one or more among seven predefined menstrual disturbances both prior to and after vaccination. In the UK survey, smoking and a history of COVID infection were associated with increased relative risk of reporting changes of menstrual cycles following vaccination against COVID-19. In our study, a low number of women had a history of COVID-19 infection, and we were unable to assess the impact of infection on menstrual disturbances, however removing these women from the analyses did not change risk estimates. The UK study did not initially aim to evaluate the impact of vaccination on menstrual cycles; however, a question was included to assess participants' perception of their menstrual cycles following vaccination at the end of the survey. Thus, no information on unvaccinated individuals was available for comparison.

In a recent preprint of a US web-based survey recruiting only vaccinated participants through Twitter and other social media platforms, 42% of people with regular menstrual cycles bled more heavily than usual, while 44% reported no change, after being vaccinated.⁹ Comparison of menstrual bleeding disorders to unvaccinated women was not possible. In a smaller Saudi-Arabian web-based survey on side-effects after COVID-19 vaccination participants were also recruited via different social media including Twitter, Snapchat, and WhatsApp. Vaccination was an inclusion criterion and participants were invited to answer an online questionnaire with prespecified adverse events. Also included was an open question for the respondent to specify any other sign not listed in the questions. Menstrual disturbances were reported in this open text field, and only a small proportion of the respondents reported abnormal menstrual cycle (delaying/increase haemorrhages or pain): 0.98% of Pfizer-BioNTech and 0.68% (7/1028) of ChAdOx1 vaccinees.¹⁰

Strengths and limitations

An assumption in the SCCS model is that the probability of being vaccinated is not affected by the occurrence of menstrual disturbances.¹¹ Although menstrual disturbances are not a contraindication for vaccination, we do not know if such events may have influenced vaccination behaviour. Recent anecdotal reports of menstrual changes after vaccination for COVID-19 may have given rise to vaccine hesitancy or refusal.

The outcomes in this study are self-reported, which has both advantages and drawbacks. There is a possibility for misclassification of past outcomes due to recall bias. The main advantage with self-reported questionnaires is that we could ask a large, representative sample simple questions to measure the occurrence of menstrual disturbances prior to and after vaccination. Using digital surveys is a safe way to perform research during the pandemic.

The linkage to the National Immunisation Registry offers an objective measure of vaccination status. The registry includes date of vaccination, which could be combined with date for filling in the electronic questionnaires to precisely estimate the time since

vaccination. The self-controlled design accounts for individual characteristics and risk factors that are constant over the study period.

Implications

These results need replication, also as part of new randomised, controlled vaccine trials. In light of the large numbers of women being exposed to COVID-19-vaccines, a causal effect on menstrual disturbances may have widespread consequences. It will be important to understand the underlying, biological mechanisms.¹² Further follow-ups in cohorts are needed to assess the proportion of women who may have longstanding problems with potential consequences for reproductive function.

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	n	%
Vaccination		
No	88	1.5
1 dose	388	6.8
2 doses	5212	91.6
Menstruating		
Yes	4054	71.3
No	1510	26.5
Don't know/missing	124	2.2
Year of birth		
1991-1994	2728	48.0
1995-1998	1959	34.4
1999-2003	1001	17.6
Type of vaccine, first dose		
Comirnaty	3295	57.9
Spikewax	2020	35.5
Other	285	5.0
No vaccine	88	1.5
Type of vaccine, second dose		
Comirnaty	2473	43.5
Spikewax	2736	48.1
Other	1	0.0
No vaccine	478	8.4

Table 1 Characteristics of 5688 women aged 18-30 taking part in the Norwegian Young Adult Cohort Study

Disturbance	Last cycle before first vaccine dose		First cycle after first vaccine dose	
	N	%	N	%
More heavy bleeding				
Yes	301	7.6	541	13.6
No	3456	87.0	3153	79.4
Don't know/missing	215	5.4	278	7.0
Prolonged bleeding				
Yes	368	9.3	498	12.5
No	3416	86.0	3227	81.2
Don't know/missing	188	4.7	247	6.2
Short interval				
Yes	376	9.5	478	12.0
No	3350	84.3	3220	81.1
Don't know/missing	246	6.2	274	6.9
Long interval				
Yes	411	10.3	432	10.9
No	3296	83.0	3266	82.2
Don't know/missing	265	6.7	274	6.9
Spot bleeding				
Yes	549	13.8	563	14.2
No	3243	81.6	3181	80.1
Don't know/missing	180	4.6	228	5.7
More pain during menstruation				
Yes	451	11.4	579	14.6
No	3323	83.7	3135	78.9
Don't know/missing	198	5.0	258	6.5
Period pain without bleeding				
Yes	725	18.3	627	15.8
No	3056	76.9	3100	78.0
Don't know/missing	191	4.8	245	6.2
Other symptoms from pelvic region				
Yes	252	6.3	199	5.0
No	3469	87.3	3496	88.0
Don't know/missing	251	6.3	277	7.0

Table 2 Disturbances during the last menstrual cycle before and the first menstrual cycle after the first vaccine dose, among women aged 18 to 30 years participating in the Norwegian Young Adult Cohort, n=3972

Disturbance	Last cycle before second vaccine dose		First cycle after second vaccine dose	
	N	%	N	%
More heavy bleeding				
Yes	287	8.2	538	15.3
No	2975	84.8	2731	77.9
Don't know/missing	245	7.0	238	6.8
Prolonged bleeding				
Yes	289	8.2	503	14.3
No	2988	85.2	2769	79.0
Don't know/missing	230	6.6	235	6.7
Short interval				
Yes	278	7.9	449	12.8
No	2969	84.7	2798	79.8
Don't know/missing	260	7.4	260	7.4
Long interval				
Yes	294	8.4	369	10.5
No	2968	84.6	2883	82.2
Don't know/missing	245	7.0	255	7.3
Spot bleeding				
Yes	350	10.0	529	15.1
No	2939	83.8	2762	78.8
Don't know/missing	218	6.2	216	6.2
More pain during menstruation				
Yes	343	9.8	561	16.0
No	2927	83.5	2699	77.0
Don't know/missing	237	6.8	247	7.0
Period pain without bleeding				
Yes	411	11.8	579	16.5
No	2859	81.5	2697	76.9
Don't know/missing	237	6.8	231	6.6
Other symptoms from pelvic region				
Yes	150	4.3	188	5.4
No	3094	88.2	3039	86.7
Don't know/missing	263	7.5	280	8.0

Table 3 Disturbances during the last menstrual cycle before and the first menstrual cycle after the **second** vaccine dose, among women aged 18 to 30 years participating in the Norwegian Young Adult Cohort, n=3507

	Number of events				
	N	Prior to vaccination	After vaccination	RR	95% CI
More heavy bleeding					
Dose 1	634	273	518	1.90	1.69–2.13
Dose 2	557	270	496	1.84	1.66–2.03
Prolonged bleeding					
Dose 1	636	335	488	1.46	1.31–1.61
Dose 2	541	274	469	1.71	1.55–1.89
Short interval					
Dose 1	603	346	456	1.32	1.19–1.46
Dose 2 dose	488	269	421	1.57	1.42–1.73
Long interval					
Dose 1	594	389	415	1.07	0.97–1.17
Dose 2	434	278	346	1.24	1.13–1.37
Spot bleeding					
Dose 1	725	502	547	1.09	1.01–1.17
Dose 2	559	330	492	1.49	1.37–1.62
More pain during menstruation					
Dose 1	706	417	563	1.35	1.24–1.47
Dose 2	582	321	521	1.62	1.49–1.77
Period pain without bleeding					
Dose 1	830	667	608	0.91	0.86–0.97
Dose 2	583	388	527	1.36	1.27–1.45
Other symptoms from pelvic region					
Dose 1	276	227	189	0.83	0.75–0.93
Dose 2	206	143	178	1.24	1.11–1.40

Table 4 Number of menstrual disturbances before vaccination and after vaccination, and relative risk (RR) of menstrual disturbances according to vaccination in the restricted sample (N) of women who had experienced the disturbance in question, for the first and second vaccine dose respectively.