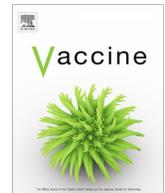




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Menstrual disturbances in 12- to 15-year-old girls after one dose of COVID-19 Comirnaty vaccine: Population-based cohort study in Norway



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1. Introduction

A worldwide COVID-19 mass vaccination campaign targeting adults was launched in late December 2020. Subsequently, the Comirnaty (BNT162b2) vaccine was recommended for children aged 12–15 years in May 2021 [1]. In Norway, only one dose of the Comirnaty vaccine was recommended to children aged 12–15 years. Vaccination was not recommended for children who had been infected with SARS-CoV-2. In line with findings in older age groups, the most prevalent adverse events after vaccination that have been reported in 12- to 15-year-old adolescents are injection site pain (in 79 to 86 % of participants), fatigue (in 60 to 66 %), and headache (in 55 to 65 %) [2]. Adolescents aged 12–17 years have been found to have a moderately higher risk of adverse reactions than adults [3].

For new vaccines, clinical trials typically collect data on commonly recognized adverse events and safety profiles. However, questions about the menstrual cycle have not been included in clinical studies. A significant number of reports on menstrual disturbances after COVID-19 vaccination have been registered in spontaneous adverse events surveillance systems in several countries (USA, UK, Norway, the Netherlands) [4–7]. Since June 2021, the Norwegian Medicines Agency has received such reports through their routine surveillance system for adverse effects of medications and vaccines [4]. Upon media attention, an increasing number of reports were received during the summer of 2021. The Netherlands Pharmacovigilance Centre Lareb reported a signal for COVID-19 vaccine-related menstrual disturbances and for post-menopausal bleeding after COVID-19 vaccination [7]. In October 2022, The European Medicines Agency (EMA) also recommended to add heavy menstrual bleeding to the product information as a possible side effect of the mRNA COVID-19 vaccines Comirnaty and Spikevax [8]. Since unverified claims of adverse effects may give rise to vaccine hesitancy or refusal, accurate scientific investigation of these phenomena is imperative for public health, also in young teenage girls.

In a recent study, we showed that women aged 18–30 years experienced menstrual cycle changes after COVID-19 vaccination [9], but importantly, such changes were also common prior to vaccination. The aim of the current study was to estimate the association between COVID-19 vaccination and menstrual disturbances in girls aged 12–15 years using maternal questionnaire responses in a large population-based cohort.

2. Methods

2.1. Study population

The Norwegian Mother, Father and Child Cohort Study (MoBa) is an ongoing population-based pregnancy cohort study established by the Norwegian Institute of Public Health. Participants were recruited during pregnancy from all over Norway during 1999–2008 [10]. The participation rate was 41 % among all invited women. The cohort now includes approximately 114 000 children and their parents, who are followed up with regular questionnaires and registry linkages. MoBa was established with the overall aim to understand causes of diseases.

Since March 2020, all active adult cohort participants (about 149 000) have also been invited to answer short electronic questionnaires every 14 days regarding symptoms related to COVID-19 disease and vaccination, life situation during the pandemic, and more. The response rate over the first 50 survey rounds during the pandemic was 46–80 %, with an average (mean) response rate of 66 %. Participation has been stable throughout the pandemic. For instance, the average participation rate was 71 % for the first ten rounds (March to August 2020), and 68 % for rounds 31–40 (May to September 2021).

In the 41st questionnaire round in autumn 2021, a subsample of participating MoBa mothers with one child aged 12–15 years (n = 29 959) were invited to answer an electronic questionnaire on behalf of their child. The questionnaire included questions about (in chronological order) COVID-19 symptoms, testing, and adverse events after vaccination. The questionnaire was distributed via text message to the mothers' mobile phones on October 13, 2021. The response rate was 64 %. Using each participant's (mother's and child's) unique national identification number, the

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questionnaire data and information from MoBa were linked to the Norwegian Immunization Registry (SYSVAK) and the National Surveillance System for Communicable Diseases (MSIS) [11]. It is mandatory for health care workers providing the vaccine to report vaccinations against COVID-19 electronically to SYSVAK, and for laboratories to report polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection to MSIS. During the fall of 2021, when children went back to school after the summer holidays in Norway, extensive testing and screening against SARS-CoV-2 was performed, due to a surge in circulation of the Delta variant.

From the group of 19 310 questionnaire respondents, we excluded 9947 boys and 1646 non-menstruating girls (Fig. 1). We also excluded 152 individuals who had received two doses of COVID-19 vaccine or were vaccinated before August 1, 2021, under the assumption that they likely belonged to a risk group due to underlying disease. Thus, the study sample consisted of 7565 girls who had started to menstruate (Fig. 1).

2.2. Exposure

Date of vaccination for each girl was obtained from the records in the national vaccine registry SYSVAK. We categorized subjects into two main groups: *Vaccinated* subjects included girls who were vaccinated between August 1st and the date of questionnaire completion, while *unvaccinated* subjects were girls who were not vaccinated upon completion of the questionnaire.

2.3. Outcomes

Questions about menstrual disturbances were posed to all mothers of girls who had started to menstruate (Supplementary Table 1). For vaccinated girls, the mothers were asked whether their daughters had experienced any of the following disturbances in their last menstruation *before* the first vaccine dose: 1) heavier bleeding than usual, 2) prolonged menstruation, 3) shorter interval between menstruations than usual, 4) longer interval between menstruations than usual, 5) spot bleedings between menstruations, 6) stronger pain during menstruation, 7) period pain without bleeding, and 8) any other symptoms from the pelvic region. Subsequently, they were asked the same list of questions for their first menstrual cycle *after* the first vaccine dose (Supplementary Table 1). Mothers of girls who had not yet had a menstrual cycle after vaccination were recommended to answer “don't know” for any of the post-vaccination disturbances. Mothers of unvaccinated

girls were asked to answer the same list of questions for their daughter's last menstruation.

2.4. Other variables

Other variables included PCR-confirmed SARS-CoV-2 infection (MSIS), the mother's vaccination status (obtained from SYSVAK) and her education level, which was self-reported in August 2021. For those with missing information on education from 2021 (about 20 %), we used the most recent available self-reported record of education level from the existing MoBa database. The girl's birth year was obtained from The Medical Birth Registry of Norway. From a questionnaire subsequently distributed to mothers in April 2022, we obtained information about use of a period tracker app (or similar). The question was asked as follows: “Is she using an app/calendar/diary/other method to track her menstruation?” (No/Yes/Not sure/Not relevant) and if Yes, “For how long has she been using this?” (<1 year, 1–2 years, >2 years, Not sure). Those answering “Yes” and duration of use “1–2 years” or “>2 years” were defined as menstrual app users to ensure that the girls had been using the app for several months prior to vaccination.

2.5. Statistical analyses

We used a self-controlled case series (SCCS) analysis to estimate associations between COVID-19 vaccination and menstrual disturbances [12]. In this design, only vaccinated cases with the outcome in question (i.e., a menstrual disturbance event before and/or after vaccination) were included. Cases who reported “don't know” or with no answer (missing) before and/or after vaccination were excluded. The cases were their own control in the sense that we compared the girl's risk of the outcome within a specified exposure window against the risk in a non-exposed window. We used the first cycle after vaccination as the window of exposure and the last cycle prior to vaccination as the non-exposed window. We chose the SCCS analysis and not a comparison between vaccinated and unvaccinated subjects because we considered the SCCS design less prone to selection and information bias in this setting. 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. We also performed the SCCS analysis stratified by age (12–13 and 14–15 years) and on a subsample (n = 1006) who had been using an app, calendar, diary or other method to track

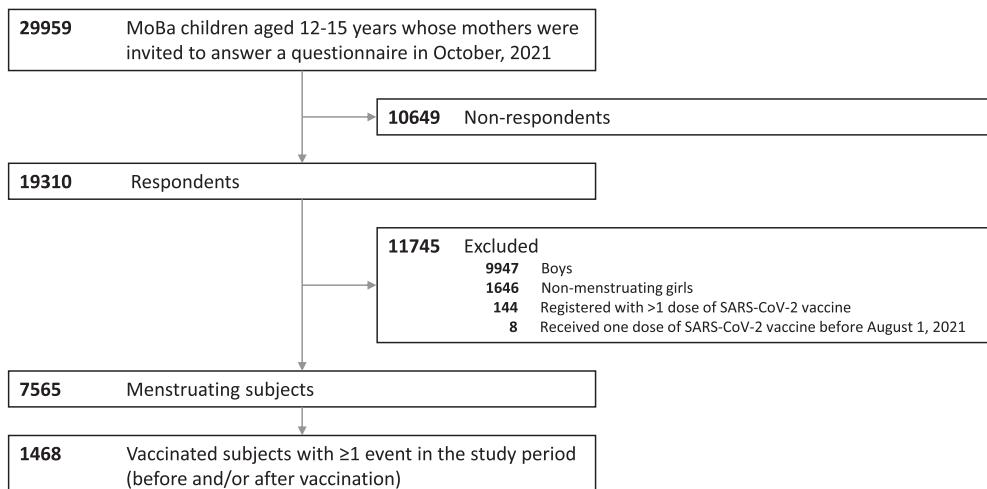


Fig. 1. Inclusion of individuals in the study.

their menstrual cycle prospectively. In a sensitivity analysis, we excluded $n = 22$ subjects with a previous SARS-CoV-2 infection from the SCCS analysis.

The median time between vaccination and completion of the questionnaire was 27 days (interquartile range 22–30, 95th percentile 37 days). Between 19.7 % and 22.3 % of mothers of vaccinated girls answered “don’t know” or did not answer questions about irregularities for their first period after vaccination. Absolute and relative risks were therefore estimated after excluding these subjects, based on the assumption that a large proportion of these girls had not yet experienced a menstrual period after vaccination.

Statistical analyses were done in Stata/SE 16.0 (Stat Corp) and R [13], version 4.1.0 [14].

2.6. Ethics

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The current sub-study was approved by The Regional Committee for Medical and Health Research Ethics, South East Norway C, no. 127708.

3. Results

About four out of five (6196 out of 7565, 81.9 %) menstruating girls had received one dose of a COVID-19 vaccine at the time of questionnaire completion (Table 1). Nearly all vaccinated girls (99.9 %) were registered with the Comirnaty vaccine, while only nine girls were registered with Vaxzevria or Spikevax as the first dose. Almost all mothers of vaccinated girls were themselves vaccinated (99.6 %). Among mothers of unvaccinated girls, about 90 % were vaccinated (Table 1). Only 1.5 % of the vaccinated girls had previously had a laboratory confirmed SARS-CoV-2 infection, compared to 28.0 % of the unvaccinated girls. In mother-daughter pairs where both were unvaccinated ($n = 144$ pairs), the mother tended to be younger and have a lower level of education than in pairs where both were vaccinated ($n = 6173$ pairs), Supplementary Table 2.

Notably, menstrual irregularities were relatively common in this sample of 12–15-year-old girls, independent of vaccination

and infection status (Table 2). The proportion of vaccinated subjects who reported one or more menstrual irregularities in their last period *prior* to vaccination was 22.6 %. In comparison, 25.1 % of this group reported at least one event for the first cycle *after* vaccination. Of these, one single menstrual irregularity (for instance, unusually heavy bleeding) was reported by 14.2 %, two different irregularities were reported by 6.1 %, and three irregularities by 2.8 %. Only 2.0 % reported four irregularities or more in the first cycle after vaccination (data not shown). In a subsample using an app or similar method to track their menstruation, the proportions reporting irregularities were slightly higher, both before and after vaccination (Supplementary Table 3). Unvaccinated girls with a history of SARS-CoV-2 infection reported more menstrual disturbances compared to unvaccinated girls with no reported infection (Table 2). Vaccinated girls had more than twofold increased risk of reporting heavy menstrual bleeding and prolonged bleeding after vaccination compared to the last cycle for unvaccinated subjects (Table 2).

In the SCCS analyses, we found that the risk of heavier menstrual bleeding and prolonged bleeding was higher in the menstrual cycle after vaccination than in the cycle before vaccination, RRs 1.61 (95 % CI 1.43 to 1.81) and 1.40 (95 % CI 1.23 to 1.60), respectively (Table 3). Vaccination was also associated with increased risk of shorter interval, longer interval, and stronger period pains (RRs 1.14 to 1.19). The effect sizes were of similar magnitude among girls aged 12–13 years and girls aged 14–15 years, and among those who were prospectively (with regard to vaccination) tracking their menstruation using an app or other method. There was no association between vaccination and spot bleeding, period pains without bleeding, or other symptoms from the pelvic region (Table 3). The risks were similar after excluding $n = 22$ subjects with a history of SARS-CoV-2 from the analysis sample (Supplementary Table 4).

4. Discussion

In this study of adolescent girls, we found increased risks of menstrual disturbances in the first cycle after receiving one dose of COVID-19 vaccine. The risks of heavier or more prolonged bleeding than usual were significantly higher in the first menstrual cycle after vaccination than in the last cycle prior to vaccination. We also found increased risks of shorter interval, longer interval and more

Table 1
Background characteristics of the study population, including 7 565 girls aged 12–15 years.

	Vaccinated with 1 dose of COVID-19 vaccine ^a ($n = 6196$)		Unvaccinated ($n = 1369$)	
	n	%	n	%
Birth year				
2006	2393	38.6	451	32.9
2007	2198	35.5	484	35.4
2008	1368	22.1	354	25.9
2009	223	3.6	79	5.8
Missing	14	0.2	1	0.1
Maternal level of education				
< High school	251	4.1	79	5.8
High school	1349	21.8	367	26.8
College ≤ 4 years	2700	43.6	569	41.6
>4 years college	1758	28.4	320	23.4
Missing	138	2.2	34	2.5
Maternal COVID-19 vaccination status				
Vaccinated	6173	99.6	1225	89.5
Unvaccinated	23	0.4	144	10.5
History of laboratory confirmed SARS-CoV-2 infection				
Yes	94	1.5	384	28.0
No	6102	98.5	985	72.0

^a Nearly all (99.9%) were vaccinated with the mRNA Comirnaty (BNT162b2) vaccine, which was recommended for children with no history of SARS-CoV-2 infection.

Table 2

Number of menstrual disturbance events reported for menstruating girls aged 12–15 years, according to COVID-19 vaccination (single dose) and SARS-CoV-2 infection status.

	Vaccinated ^a (n = 6196)				Unvaccinated, no SARS-CoV-2 infection (n = 985)		Unvaccinated, history of SARS-CoV-2 infection (n = 384)	
	Event registered for last cycle before vaccine		Event registered for first cycle after vaccine ^b		Event registered for last cycle		Event registered for last cycle	
	n	% ^c	n	% ^c	n	% ^c	n	% ^c
Any menstrual disturbance event^d								
Yes	1054	22.6	1091	25.1	165	22.3	95	33.0
No	3619		3251		576		193	
Don't know	1385		1733		217		90	
Missing ^e	138		121		27		6	
Heavier bleeding								
Yes	235	4.7	333	7.3	22	2.8	15	5.1
No	4757		4198		773		280	
Don't know	1147		1635		178		86	
Missing	57		30		12		3	
Prolonged bleeding								
Yes	199	3.9	245	5.4	16	2.0	12	4.0
No	4844		4302		789		291	
Don't know	1086		1617		165		78	
Missing	67		32		15		3	
Shorter interval								
Yes	269	5.5	285	6.3	39	4.9	21	7.0
No	4658		4227		755		278	
Don't know	1194		1643		176		81	
Missing	75		41		15		4	
Longer interval								
Yes	376	7.7	339	7.5	65	8.2	51	16.7
No	4516		4160		725		255	
Don't know	1238		1650		178		75	
Missing	66		47		17		3	
Spot bleeding								
Yes	153	3.1	142	3.1	24	3.0	9	3.0
No	4836		4470		785		289	
Don't know	1139		1534		162		82	
Missing	68		50		14		4	
Stronger period pains								
Yes	333	6.4	326	6.9	59	6.9	23	7.3
No	4879		4381		795		294	
Don't know	918		1449		118		64	
Missing	66		40		13		3	
Period pains without bleeding								
Yes	292	5.8	244	5.2	42	5.1	25	8.3
No	4741		4411		782		277	
Don't know	1096		1500		148		79	
Missing	67		41		13		3	
Other symptoms from the pelvic region								
Yes	42	0.8	38	0.8	8	1.0	4	1.3
No	4998		4645		804		294	
Don't know	1096		1470		160		82	
Missing	60		43		13		4	

^a Vaccinated subjects had received one dose of COVID-19 vaccine.^b Median time between vaccination and completion of the questionnaire was 27 days (interquartile range 22–30).^c Proportions were calculated based on valid answers ("yes" and "no"), excluding "don't know" and missing answers.^d "Yes" includes subjects with at least one event reported. "No" includes subjects answering "no" for all events.^e "Missing" includes subjects with at least one missing answer across all events.

pain during periods following vaccination. Notably, menstrual irregularities were common also prior to vaccination and among unvaccinated subjects. For most girls, no changes were reported following COVID-19 vaccination.

Our study design has several strengths. We use a large population-based cohort, with recruitment many years prior to the exposures. The representativeness of MoBa has previously been studied, indicating a somewhat higher socio-economic status among participants than in the general Norwegian population [15,16]. In the SCCS analyses, differences in time invariant factors, such as genetics, socio-economic status, or underlying diseases, are cancelled out, which reduces bias [12]. This design should therefore

provide more valid risk estimates than a design comparing different subgroups (i.e., vaccinated vs unvaccinated subjects). Another strength of the study is that information on both vaccination and SARS-CoV-2 infection status was obtained from nationwide registries with mandatory reporting. Although self-reported data collection could be subjected to bias, using digital surveys is a safe way to perform research during the pandemic and valuable in a situation where many are vaccinated in a short period. Moreover, responding mothers have participated in MoBa for more than a decade and are accustomed to answering questionnaires, also on behalf of their child. The questionnaire used in the current study was not solely focused on vaccination and menstruation but cov-

Table 3

Risk of menstrual disturbances during the first cycle after vaccination compared to the last cycle prior to vaccination among n = 1468 vaccinated girls aged 12–15 years and in a subsample who reported use of a menstruation app (or similar) at least 6 months prior to vaccination^a. Relative risks (RR) were estimated using a self-controlled case series analysis, for girls who experienced any menstrual changes prior to and/or after vaccination.

	Age group (years)	No. of subjects	No. of events		RR (95 % CI)
			Prior to vaccination	After vaccination	
Heavier bleeding					
	12–15 ^b	369	197	316	1.60 (1.43 to 1.80)
	12–13 ^c	87	46	76	1.65 (1.30 to 2.10)
	14–15 ^d	282	151	240	1.59 (1.39 to 1.82)
	12–15, app users	74	43	68	1.58 (1.27 to 1.97)
Prolonged bleeding					
	12–15	279	163	227	1.39 (1.22 to 1.59)
	12–13	73	46	61	1.33 (1.05 to 1.67)
	14–15	205	116	166	1.43 (1.22 to 1.68)
	12–15, app users	51	32	45	1.41 (1.09 to 1.82)
Shorter interval					
	12–15	338	228	272	1.19 (1.07 to 1.32)
	12–13	87	57	70	1.23 (0.99 to 1.52)
	14–15	250	170	201	1.18 (1.05 to 1.33)
	12–15, app users	74	49	59	1.20 (0.96 to 1.51)
Longer interval					
	12–15	423	284	328	1.15 (1.05 to 1.27)
	12–13	120	79	88	1.11 (0.91 to 1.36)
	14–15	302	204	239	1.17 (1.05 to 1.31)
	12–15, app users	81	54	65	1.20 (0.97 to 1.50)
Spot bleeding					
	12–15	176	125	133	1.06 (0.92 to 1.23)
	12–13	41	27	31	1.15 (0.82 to 1.60)
	14–15	133	96	101	1.05 (0.89 to 1.24)
	12–15, app users	38	24	29	1.21 (0.85 to 1.72)
Stronger period pains					
	12–15	388	271	310	1.14 (1.04 to 1.26)
	12–13	71	51	60	1.18 (0.97 to 1.43)
	14–15	316	219	249	1.14 (1.02 to 1.27)
	12–15, app users	67	48	55	1.15 (0.93 to 1.42)
Period pains without bleeding					
	12–15	315	240	240	1.00 (0.90 to 1.11)
	12–13	80	56	61	1.09 (0.87 to 1.36)
	14–15	235	184	179	0.97 (0.87 to 1.09)
	12–15, app users	59	42	46	1.10 (0.86 to 1.40)
Other symptoms from the pelvic region					
	12–15	49	38	37	0.97 (0.76 to 1.25)
	12–13	18	12	14	1.17 (0.72 to 1.88)
	14–15	31	26	23	0.88 (0.66 to 1.18)
	12–15, app users	4	3	3	1.00 (0.40 to 2.52)

^a Among n = 7565 menstruating subjects in the study sample, n = 4455 (59 %) had answered a questionnaire in April 2022 (i.e., approximately 6 months after collection of menstrual data), which included questions about menstruation registration. The question asked was "Is she using an app/calendar/diary/other method to log her menstruation?" and if Yes, "For how long has she been using this?". Subjects who reported use of a menstruation registration method for at least 1 year were included in this subsample, referred to as "app users".

^b Birth year 2006–2009.

^c Birth year 2008–2009.

^d Birth year 2006–2007.

ered other aspects of the pandemic, which may have reduced selection bias for menstruation-related questions.

This study also has some limitations that need to be addressed. First, mothers were reporting on behalf of their daughters, which may have introduced misclassification, likely underreporting, of the outcomes. Still, the questions covered a range of symptoms potentially related to both infection and vaccination (such as respiratory symptoms, headache, dizziness, unwellness, skin rash, and more), which warranted close communication between mother and daughter as a basis for answering the questionnaire. Second, the occurrence of menstrual disturbances both *before* and *after* vaccination was reported by mothers at the same timepoint. Therefore, we cannot rule out that the mother's report of irregularities before vaccination is biased by the outcome after vaccination. Still, our findings seem relatively robust to recall bias, as similar relative risks were estimated for a subsample who used a menstruation app or similar method to track their menstruation. Third, the media's emphasis on a potential link between menstrual cycle irregu-

larities and COVID-19 vaccination may have increased the awareness among vaccinated participants, thus increasing the likelihood of them reporting such events after vaccination [17]. Indeed, in this study, some menstrual disturbances were reported more often for vaccinated girls compared to unvaccinated girls even *before* they were vaccinated. This may indicate that mothers of vaccinated girls, or the vaccinated girls themselves, are more aware about menstrual irregularities and the potential adverse events after COVID-19 vaccination. The increased awareness may potentially have introduced some information bias to our analysis but probably to a limited extent for the estimated relative risks since our subjects act as their own controls. Also, the lack of association between vaccination and spot bleeding, period pains without bleeding, or other symptoms from the pelvic region, may support that bias does not solely explain the associations seen for the other outcomes. Lastly, the interval between vaccination and the date of responding to the questionnaire may have been too short to allow detection of the outcomes in all girls, especially the outcome

“longer interval”, and some girls probably did not have time to experience a menstruation after vaccination. We cannot rule out that this outcome may be prone to information bias due to this limitation. Also, the exclusion of subjects answering “don’t know” in the SCCS analysis may potentially introduce bias if the occurrence of menstrual disturbances is different in this group before and after vaccination.

The reports concerning irregularities in the menstrual cycle after receiving mRNA COVID-19 vaccines among women have been widely discussed [18,19]. Menstrual disturbances are more common after COVID-19 vaccines than after non-COVID-19 vaccines in VAERS reports [19]. A study from the US reported that COVID-19 vaccination was associated with a small change in cycle length but not menses length [20]. In an online questionnaire with participants from Saudi-Arabia, one per cent of female participants (broad age groups) who had received the Comirnaty vaccine reported abnormal menstrual cycle as a post-vaccinal short term adverse event, in an open field (i.e., the outcome was not listed as a response alternative) [21]. In data collected in the UK prior to the widespread media attention to menstrual disturbances following COVID-19 vaccination, one study found that among menstruating, pre-menopausal, vaccinated individuals, 20 % reported changes to their menstrual cycles up to 4 months after receiving their first vaccine dose [22]. A prospectively recruited cohort with 79 individuals showed that COVID-19 vaccine is associated with a delay to the subsequent period, and interestingly detected no association between menstrual changes and other commonly-reported side effects [23]. In a large survey from the US (median age 33 years), increased bleeding appeared to be the most common post-vaccination adverse events [24]. Moreover, a recent large study from our group observed an increased risk of menstrual disturbances after vaccination in women aged 18–30 years, both after the first and after the second vaccine dose [9]. However, another study from the UK using a retrospective recruitment did not find any association between COVID-19 vaccination and menstrual disturbances [25]. The results in our current study therefore lie within the (wide) range of estimates reported in the existing, though limited, data on adults. Given the lack of data for adolescents in particular, our findings need to be confirmed in other studies.

There have also been indications that infection with SARS-CoV-2 may cause changes in the menstruation cycle [18,26,27]. It has been proposed that since ACE2 receptors are present on ovarian and endometrial tissue, SARS-CoV-2 infection may exert a direct impact on the female reproductive system [26,27]. In the current study, we observed a higher occurrence of menstrual disturbances among unvaccinated girls with a previous SARS-CoV-2 infection compared to uninfected girls in the unvaccinated group. However, our study was not designed to evaluate menstrual disturbances after SARS-CoV-2 infection and this observation needs to be confirmed in other studies. Also, whether menstrual disturbances are equally common after SARS-CoV-2 infection and vaccination should be elucidated. COVID-19 vaccination and infection may potentially influence the menstruation cycle through a similar mechanism involving ACE2 receptors. The vaccine activates the immune system, possibly attacking immune cells and inflammatory molecules in the uterus [28]. Thus, some studies suggest that vaccination is less likely to affect menstruation via ovarian hormone pathways, and more likely along the inflammatory pathways [20,24,29]. Still, the pathophysiological mechanisms are yet unknown.

Assessment of the safety aspects are important when deciding on whether to vaccinate children or not since children seldom get seriously ill with SARS-CoV-2-infection [2]. After the rapid development and emergency authorization of SARS-CoV-2 vaccines, serious adverse reactions have been reported more frequently for the SARS-CoV-2 vaccines in comparison to other vaccines, such

as influenza vaccines [6]. Careful evaluation of the short- and long-term effects of both the infection itself, as well as the vaccine used for prevention, should always be performed when evaluating new vaccines. This is highly actualized during the COVID-19 pandemic where long-term consequences of SARS-CoV-2 infection are becoming evident and mass vaccination campaigns with vaccines based on new technologies have been rolled out quickly and in the similar time frame. Although the COVID-19 vaccine has become available to children, not all countries have recommended a second dose or have delayed the recommendation for safety issues. Understanding the risk of adverse reactions associated with the vaccine will assist parents in making an informed decision on whether their child should get vaccinated or not, or how many doses. The safety risk must be weighed against the risk of disease from the virus and may change depending on the circulating viral variant. Despite many reports of altered menstrual bleeding patterns after vaccination, it is still not possible to exclude the possibility that these might reflect normal variation amongst the millions of individuals that have had SARS-CoV-2 infections and received COVID-19 vaccine.

To our knowledge, this is the first study to estimate the risk of menstrual disturbances after COVID-19 vaccination in adolescents. More data collected in real-time is needed to confirm our findings and to assess the risk of recurrence after a second dose in this age group. Also, studies exploring potential mechanisms are warranted. Studies that assess the direct effect of vaccination on the menstrual cycle are few and far between. Therefore, a continuous monitoring of COVID-19 vaccines is essential to enhance the reassurance and acceptance of COVID-19 vaccinations in all age groups.

5. Conclusions

In this population-based study conducted in Norway, vaccination against COVID-19 for adolescent girls was associated with increased risk of experiencing menstrual disturbances in the first cycle after vaccination. However, most young girls reported no changes to their menstrual cycle following COVID-19 vaccination. Nearly all adolescent girls in Norway received one dose of the Comirnaty vaccine, which should be considered in the interpretation of our findings.

Contributors

IHC and LKJ are co-first authors and contributed equally to this study. LT and PM designed the study and collected the data. All authors contributed to the study conceptualization and methods. IHC, LKJ, BF, and IL had full access to all the data and performed statistical analyses. All authors interpreted the data. IHC, LKJ and LT prepared the first draft of the manuscript. All authors revised the manuscript, approved the final version. Co-first authors IHC and LKJ had final responsibility for the decision to submit for publication.

Data statement

Data from the cohort is available for analysis after approval from a Norwegian ethics committee and application to the Norwegian Institute of Public Health.

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Data availability

Data from the cohort is available for analysis after approval from a Norwegian ethics committee and application to the Norwegian Institute of Public Health.

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 data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2022.11.068>.

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