

# COVID-19 vaccine and Menstrual conditions in female: data analysis of the Vaccine Adverse Event Reporting System

Bing Zhang (✉ [13553186269@163.com](mailto:13553186269@163.com))

Shandong University of Traditional Chinese Medicine

Xiao Yu

Affiliated Hospital of Shandong University of Traditional Chinese Medicine

Jinxing Liu

Affiliated Hospital of Shandong University of Traditional Chinese Medicine

Pengfei Liu

Affiliated Hospital of Shandong University of Traditional Chinese Medicine

---

## Research Article

**Keywords:** VAERS, COVID-19 vaccine, Menstrual disorders events, 30-49 years, Risk signals

**Posted Date:** April 7th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1388159/v2>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Background:** In reports of adverse reactions following vaccination with the coronavirus disease 2019(COVID-19) vaccines, there have been fewer reports of concern for menstrual disorders in female. **Objective:** Our study used Vaccine Adverse Event Reporting System(VAERS)to investigate and analyze the relationship between COVID-19 Vaccines and menstrual disorders in female. **Methods:** We collected reports of menstrual disorders in VAERS from July 2, 1990 to November 12, 2021, and performed a stratified analysis. The potential relationship between COVID-19 vaccine and reports of menstrual disorders was evaluated using the Reporting Odds Ratio (ROR) method. **Results:** A total of 14,431 reports of menstrual disorders were included in the study, and 13,118 were associated with COVID-19 vaccine. The ROR was 7.83 (95% confidence interval [95%CI]:7.39-8.28). The most commonly reported event was Menstruation irregular (4998 reports), and a higher percentage of female aged 30-49 years reported menstrual disorders (42.55%) after exposure to COVID-19 Vaccines. Both for all reports of menstrual disorders (ROR=5.82; 95%CI:4.93-6.95) and excluding reports of unknown age (ROR=13.02; 95%CI:10.89-15.56), suggest that female age may be associated with menstrual disorders after vaccination with the COVID-19 Vaccines. **Conclusion:** Our study suggests a potential safety signal among female who received the COVID-19 vaccine, which may cause menstrual disorders in young adult female (30-49 years old). However, due to the well-known limitations of spontaneous reporting data, it is challenging to directly define menstrual disorders as an adverse event of the COVID-19 Vaccines, and reports of adverse reactions to COVID-19 Vaccines in this age group should continue to be tracked.

## Impacts On Practice

1. After the launch of the COVID-2019 vaccine, much attention has been focused on special populations, such as: elderly, children, pregnant women, and even congenital allergies, while less attention is paid to reports of adverse reactions in adult women after vaccination.
2. The proportion of women aged 30–49 years reporting menstrual disorders after vaccination has risen, and reports of adverse reactions in this age group in women should continue to be monitored.

## Background

Coronavirus disease of 2019<sup>[1]</sup> (COVID-19) is a highly pathogenic viral infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 infection remains a global concern since the end of 2019 to date. According to WHO, as of January 6, 2022, 293,750,692 cases of COVID-19 have been diagnosed worldwide, and 55,972,114 cases have been diagnosed in the United States. For epidemic control, the safe and effective vaccine is the long-term solution to control the COVID-19 global pandemic<sup>[2]</sup>. Research studies<sup>[3]</sup> have shown that an average vaccination level of about 80 doses per 100 inhabitants between countries can sustain a reduction in the number of confirmed cases and deaths. The recent emergence of the Omicron variant further emphasizes the importance of vaccination, and prevention efforts needed to protect against COVID-19.

The FDA approved three COVID-19 vaccines for emergency use in the United States in mid-December 2020<sup>[4, 5]</sup> and late February 2021<sup>[6]</sup>, respectively. By the end of 2021, more than a dozen COVID-19 vaccines in six categories are approved for use worldwide. Local and systemic reactions were the predominant types of adverse events observed in pre-emergency authorization clinical trials of these vaccines. Because of the short development cycle of COVID-19 vaccines, there are continuing concerns about the post-marketing safety and efficacy of vaccines. In order to continue to monitor the post-marketing safety of vaccines, countries around the world have taken different measures to collect information about vaccine recipients. The Centers for Disease Control and Prevention in the United States uses the Vaccine Adverse Reaction Reporting System (VAERS) for ongoing monitoring of the safety of the COVID-19 vaccine<sup>[7]</sup>.

Since the launch of the COVID-19 vaccine, more research points have focused on special groups such as the elderly<sup>[8]</sup>, adolescents<sup>[9, 10]</sup>, and maternity<sup>[11, 12]</sup>. More attention is paid to aspects such as rare allergic reactions<sup>[13]</sup> and cardiovascular system diseases<sup>[14]</sup> after vaccination, and less attention is paid to female's menstrual conditions. The purpose of this study is to discuss the safety of COVID-19 vaccines in female based on real data spontaneously reported in the VAERS and to attempt to analyze the potential relationship between COVID-19 vaccines and trends in reporting of menstrual disorders.

### **Aim of the study**

The purpose of this study was to detect signals of menstrual disorder-like adverse reactions after COVID-2019 vaccination using the US Vaccine Adverse Event Reporting System (VAERS) database.

## **Method**

### **Database**

Established in 1990, VAERS<sup>[15]</sup> (<https://vaers.hhs.gov/>) is a system for spontaneous and voluntary reporting of any suspected adverse drug reactions (ADRs) associated with vaccine use, jointly administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). The primary purpose of VAERS is to detect early signals and generate hypotheses about possible new vaccine adverse events that were not identified in premarketing trials. VAERS accepts reports from vaccine recipients, parents, health care providers, vaccine manufacturers, and others. The VAERS report form collects information about the individual who received the vaccine, the type number of vaccine received, and the adverse reaction itself.

Signs and symptoms of adverse reaction are coded using the Medical Dictionary of Regulatory Activities (MedDRA)<sup>[16]</sup>. A single VAERS report can contain multiple MedDRA preferred terms. The following reports are categorized as "serious" reports under the US Code of Federal Regulations<sup>[17]</sup>: Hospitalization, Prolonged hospitalization, Emergency room visits, Disability, Life-threatening, or Death.

### **Dataset**

After removing sensitive patient information, the original data files were downloaded from the VAERS website in comma-separated value (CSV) format. We downloaded the dataset in VAERS from the 1990 build through November 12, 2021, both U.S. regions and non-U.S. regions. The dataset consists of three separate data files for data, vaccines, and symptoms.

## Data Selection

Use navicat15 for data mining. The following strategy was used:(1) Exclude all reports of male and unknown gender. Search for the following MedDRA preferred terms: "Menstruation irregular" "Menstruation delayed" "Menstrual disorder" "Hypomenorrhoea" "Menorrhagia" "Intermenstrual bleeding" "Metrorrhagia" "Amenorrhoea" (2) Each report was reviewed to clarify that the menstrual disorders were not caused by pregnancy (3) The ID, type of vaccine injected, and dose of injection were checked for each report, and reports with multiple repetitions of the same ID were excluded. (4) We extracted information on ID, vaccine type, vaccine dose, age, type of menstrual disorder, patient outcome, vaccination date, reporting interval, and past history from each report. Detailed interpretation of the reports can be found in the VAERS Data Use Guide<sup>[18]</sup>.

## Data Analysis

The integration, extraction, and filtering of the reported data are performed by navicat15, and the description and statistical analysis of the data are realized by Free Statistics software version 1.4.

We summarized the basic characteristics of the reports by different types of menstrual disorders, age, reporting interval, severity, and past history, and performed a stratified analysis of age and reporting interval. Characterization of the types of menstrual disorders reported for different vaccine types, statistical analysis using Fisher's exact test. A line graph is used to indicate the trend in the type of report. The Reporting Odds Ratio (ROR)<sup>[19]</sup> was used to assess the disproportionate reporting of adverse reactions, with the lower limit of the ROR 95% confidence interval [95%CI] > 1 and a number of reports  $\geq 3$  suggesting the generation of an adverse signal. We performed the following sensitivity analyses of menstrual disorders events: (1) US and non-US regions; (2) stratification by age; and (3) exclusion of cases of unknown age.

VAERS is a self-reporting vaccine adverse reaction surveillance system that meets the definition of a study as specified in 45 CFR 46<sup>[20]</sup>. Exemptions (2018Requirements). It is not subject to Institutional Review Board review and informed consent requirements.

## Results

# Reports of Menstrual disorders in Vaccine Adverse Event Reporting System (VAERS)

Figure 1 shows the report selection process, including the reasons for exclusion. By November 12, 2021, 1742590 cases of adverse events were recorded in the VAERS database, and 60.94% of them were female. The category including menstrual disorders events 14,331 reports (1.36%), of which 13,118 (90.90%) were exposed to COVID19 vaccine and 13,13 (9.10%) were exposed to another vaccine. There were 1047452 (98.64%) other adverse events, 587325 (56.07%) were exposed to COVID-19 vaccine and 460130 (43.93%) were exposed to other vaccines.

## **Characterization of menstrual disorders events**

Table 1 describes the basic characteristics of the 14431 reported cases of menstrual disorders. Reports of menstrual disorders are not mutually exclusive of each other, and multiple conditions may be involved in one adverse reaction report. The most prevalent event in both groups was Menstruation irregular, with 4626 cases (35.26%) reported in the COVID-19 vaccine group and 372 cases (28.33%) in the non-COVID-19 vaccine group. The COVID-19 vaccine group reported 2698 cases (20.57%) of Menstruation delayed, 2088 cases (15.92%) of Intermenstrual bleeding, and Menorrhagia was reported only 28 cases (0.21%). The non-COVID-19 vaccine group reported 251 cases of Menorrhagia (19.12%), 301 cases of Amenorrhoea (22.90%) and only 6 cases of Intermenstrual bleeding (0.46%).

Table 1  
Summary of characteristics of menstrual disorders

	Total (N = 14431)		Non COVID-19 vaccine (N = 1313)		COVID-19 vaccine (N = 13118)	
	n	%	n	%	n	%
<b>Menstruation irregular event types</b>						
Menstruation irregular	4998	34.63	372	28.33	4626	35.26
Menstruation delayed	2803	19.42	105	8.00	2698	20.57
Menstrual disorder	2088	14.47	127	9.67	1962	14.96
Metrorrhagia	1922	13.32	251	19.12	1671	12.74
Amenorrhoea,	1956	13.55	301	22.92	1655	12.62
Menorrhagia	260	1.80	232	17.67	28	0.21
Hypomenorrhoea	1076	7.46	33	2.51	1043	7.95
Intermenstrual bleeding	2094	14.51	6	0.46	2088	15.92
<b>Age (years) *</b>						
Median	35	(27.0, 42.0)	16	(13.0, 24.0)	36	(30.0,43.0)
<20	926	6.46	641	48.82	285	2.17
20 ~ 29	1952	13.62	211	16.07	1741	13.27
30 ~ 39	3255	22.71	79	6.02	3176	24.21
40 ~ 49	2476	17.28	70	5.33	2406	18.34
≥ 50	568	3.96	8	0.61	560	4.27
Unknow	5254	36.66	304	23.15	4950	37.73
<b>Time between reports(days)**</b>						
Median	3	(1.0, 15.0)	8	(0.0, 49.8)	3	(1.0, 14.0)
Multiple MedRDA terms can exist in one adverse reaction report, so the sum of the individual events of menstrual disorders events may be greater than the total number of reports.						
Fisher's exact test: $\alpha = 0.05$ ,						
*P-value < 0.001,						
**P-value < 0.001						

	Total (N = 14431)		Non COVID-19 vaccine (N = 1313)		COVID-19 vaccine (N = 13118)	
	n	%	n	%	n	%
<100	11463	79.43	586	44.63	10877	82.92
100 ~ 200	123	0.85	39	2.97	84	0.64
200 ~ 300	22	0.15	21	1.60	1	0.01
≥ 300	73	0.51	60	4.57	13	0.10
Unknow	2750	19.06	607	46.23	2143	16.34
<b>Serious adverse event</b>						
Death	3		3	0.23	0	
Life-threatening	126	0.87	45	3.43	81	0.62
Emergency room visits	406	2.81	406	30.92	0	
Hospitalized	540	3.74	244	18.58	296	2.26
Prolonged hospitalization	28	0.19	14	1.07	14	0.11
Disability	877	6.08	189	14.39	688	5.24
<b>History and current</b>						
Taking medications	5526	38.56	273	20.79	5253	40.04
Current Diseases	1175	8.20	191	14.55	984	7.50
Past Diseases	6481	45.22	277	21.10	6204	47.29
Multiple MedRDA terms can exist in one adverse reaction report, so the sum of the individual events of menstrual disorders events may be greater than the total number of reports.						
Fisher's exact test: $\alpha = 0.05$ ,						
*P-value < 0.001,						
**P-value < 0.001						

The median age at the time of reporting was 35 years in both groups, with a mean age of 36 years in the COVID-19 vaccine group, which was greater than 16 years in the non-COVID-19 vaccine group. A high proportion of the reported age was unknown in both groups. Nearly half (48.82%) of the reported menstrual irregularities in the non-COVID-19 vaccine group were reported in the younger age group (< 20

years). Whereas in the COVID-19 vaccine group, a higher proportion (42.55%) was reported in the prime age group (30–49 years). After Fisher's exact test, there was a difference between the two age groups (P value < 0.001).

The interval from vaccine exposure to reported onset was reported in 11,681 cases (80.94%), with a median of 3.0 days. There were 10,877 cases (82.92%) in the COVID-19 vaccine group with an adverse reaction reporting interval < 100 days. The mean reporting interval for the non-COVID-19 vaccine group was 8 days. After Fisher's exact test, there was a difference in the reporting interval between the two groups (P value < 0.001). There are 20 non-COVID-19 vaccines associated with reported menstrual disorders, namely: Influenza virus vaccine(38 reports) □ Hepatitis B virus vaccine(51 reports) □ Tetanus and diphtheria toxoids vaccine(9 reports) □ Pneumococcal vaccine(3 reports) □ Varivax-varicella virus live(14 reports) □ Tetanus toxoid(1 report) □ Human papillomavirus(1073 reports) □ Hepatitis A (12 reports) □ Anthrax vaccine(20 reports) □ Measles(1 report) □ Measles, mumps and rubella virus vaccine(15 reports) □ Lyme disease vaccine(4 reports) □ Rabies virus vaccine(2 reports) □ Smallpox vaccine(2 reports) □ Meningococcal conjugate vaccine(3 reports) □ Hepatitis A + hepatitis B vaccine(4 reports) □ Ebola Zaire vaccine(1 report) □ Meningococcal group b vaccine(1 report) □ Varicella-zoster vaccine(1 report) □ Unknow(57 reports).

The reported species of serious adverse events were mainly related to Death, Life-threatening, Emergency room visits, Hospitalized, Prolonged hospitalization, and Disability. There were no reports of deaths in the COVID-19 vaccine group, and a total of 1079 serious adverse events were reported (8.22%). 901 serious adverse events (68.62%) were reported in the non- COVID-19 vaccine group, three deaths were reported which were the result of exposure to Human papillomavirus vaccine(2 reports) and Hepatitis B virus vaccine(1 report). More than one-third of the reports in both groups mentioned a prescription or nonprescription drugs that the vaccine recipient was taking at the time of vaccination and 1175 cases (8.20%) were suffering from a disease, while 6481 cases (45.22%) had been diagnosed with a disease prior to vaccination.

## **Characterization of different COVID-19 vaccine types**

Table 2 describes the characteristics of the 13,118 menstrual disorders reported as a result of exposure to the COVID-19 vaccine. 9613 cases (73.28%) were reported in relation to Pfizer-Biontech, 2748 cases (20.95%) for Moderna and 742 cases (5.66%) for Janssen. The reported rates of other menstrual events differed between groups ( $p < 0.001$ ), except Intermenstrual bleeding, Hypomenorrhoea, Menorrhagia. Comparison between groups revealed that the distribution of reports of menstrual disorders by age group was heterogeneous ( $p < 0.001$ ). Except for the type of vaccine that could not be specified, the remaining three groups reported significantly higher proportions in the 30–39 age group than in other age groups, respectively accounting for 19.53%, 38.54%, and 31.67% of the total. The dose distribution by injected vaccine was also heterogeneous ( $P < 0.001$ ), with Dose 1 being reported at a significantly higher rate than Dose 2 and Dose 3. Only 1596 cases (16.60%) of vaccine recipients recovered from the adverse event when the adverse reaction information was reported, and 66.33% did not recover at the time of reporting.



Table 2  
 Characterization of different COVID-19 vaccine types

	Pfizer-Biontech (n = 9613)		Moderna (n = 2748)		Janssen (n = 742)		Unknown (n = 15)	
	n	%	n	%	n	%	n	%
<b>Menstruation irregular event types</b>								
Menstruation irregular	3327	34.61	991	36.06	302	40.70	6	40.00
Menstruation delayed	2152	22.39	454	16.52	88	11.86	4	26.67
Menstrual disorder	1141	11.87	614	22.34	204	27.49	2	13.33
Metrorrhagia	1444	15.02	199	7.24	27	3.64	1	6.67
Amenorrhoea	1094	11.38	453	16.48	105	14.15	3	20.00
Menorrhagia	26	0.27	2	0.07	0	0.00	0	0.00
Hypomenorrhoea	758	7.89	220	8.01	64	8.63	1	6.67
Intermenstrual bleeding	1545	16.07	440	16.01	101	13.61	2	13.33
<b>Age (years)*</b>								
Median	36	29.0, 42.0)	36	(30.0, 43.0)	38	(31.0, 44.0)	43	(35.5, 48.2)
<20	235	2.44	37	1.35	13	1.75	0	0.00
20 ~ 29	1057	11.00	564	20.52	120	16.17	0	0.00
30 ~ 39	1877	19.53	1059	38.54	235	31.67	5	33.33
40 ~ 49	1422	14.79	749	27.26	227	30.59	8	53.33
≥ 50	288	3.00	211	7.68	60	8.09	1	6.67
Unknow	4734	49.25	128	4.66	87	11.73	1	6.67
<b>Dose**</b>								
Dose 1	4966	51.66	1388	50.51	465	62.67	9	60.00
Multiple MedRDA terms can exist in one adverse reaction report, so the sum of the individual events of menstrual disorders events may be greater than the total number of reports.								
Fisher's exact test: $\alpha = 0.05$ ,								
* P-value < 0.001								
** P-value < 0.001								

	Pfizer-Biontech (n = 9613)		Moderna (n = 2748)		Janssen (n = 742)		Unknown (n = 15)	
	n	%	n	%	n	%	n	%
Dose 2	3563	37.06	923	33.59	1	0.13	2	13.33
Dose 3	65	0.68	17	0.62	0	0.00	0	0.00
Unknown	1019	10.60	420	15.28	276	37.20	4	26.67
<b>Serious adverse event</b>								
Life-threatening	66	0.69	9	0.33	6	0.81	0	
Hospitalized	238	2.48	46	1.67	12	1.62	0	
Prolonged hospitalization	0		1	0.04	1	0.13	0	
Disability	550	5.72	117	4.26	20	2.70	1	6.67
<b>History and current</b>								
Taking medications	3441	35.80	1398	50.87	406	54.72	8	53.33
Current Diseases	587	6.11	327	11.90	68	9.16	2	13.33
Past Diseases	4874	50.70	1046	38.06	277	37.33	7	46.67
<b>Recovrd</b>								
No	6376	66.33	1465	53.31	401	54.04	7	46.67
Yes	1596	16.60	628	22.85	136	18.33	3	20.00
Unknow	1424	14.81	521	18.96	165	22.24	5	33.33
Multiple MedRDA terms can exist in one adverse reaction report, so the sum of the individual events of menstrual disorders events may be greater than the total number of reports.								
Fisher's exact test: $\alpha = 0.05$ ,								
* P-value < 0.001								
** P-value < 0.001								

## Reporting Odds Ratio

Reporting Odds Ratio analysis of reported events for the COVID-19 vaccine show as Table3 to Table6. The distribution of adverse events according to type (Menstrual disorder vs. other adverse reactions) and vaccination status (COVID-19 vaccines vs. other vaccines) is reported in Table 3. ROR estimated to be

7.83 (95% CI:7.39–8.28), suggests that COVID-19 vaccine may be a risk sign for the occurrence of events related to menstrual disorders. To further verify the correlation, three sensitivity analysis of the ROR were also performed. Firstly grouped by region of adverse reaction reporting (US vs. non-US) and vaccination status, ROR was 0.78(95% CI:0.70–0.88), suggested that the reports of menstrual disorders after vaccination with the COVID-19 vaccine are not related to the regional distribution. Secondly grouped by age and type of report, compared the reported rates of adverse events associated with menstrual disorders in the 30–49 age group with those in other age groups, ROR was 5.78(95% CI:4.86–6.88). Finally, excluding reports of unknown age, ROR was 12.46(95% CI:10.41–14.92). Suggests that age may be a risk flag for the event of menstrual disorders after vaccination with the COVID-19 vaccine.

Table 3  
Distribution of adverse events stratified by menstrual disorders events and vaccination status

	<b>Menstrual disorders events</b>	<b>Other adverse events</b>	<b>Total</b>
COVID-19 vaccine	13118	587325	600443
Other vaccines	1313	460130	461443
Total	14431	1047452	1061886
ROR = 7.83,(95%CI:7.39–8.28)			

Table 4  
Sensitivity analyses<sup>1</sup> (Distribution of adverse events stratified by region and vaccination status)

	<b>U.S.</b>	<b>Non-U.S.</b>	<b>Total</b>
COVID-19 vaccine*	6431	6687	13118
Other vaccines**	724	589	1313
Total	7155	7276	14431
*Menstrual disorders events reported after exposure to COVID-19 vaccine			
** Menstrual disorders events reported after exposure to other vaccines			
ROR = 0.78,(95%CI:0.70–0.88)			

Table 5  
Sensitivity analyses<sup>2</sup> (Distribution of adverse events stratified by age and vaccination status)

	<b>30–49 ages</b>	<b>Other ages</b>	<b>Total</b>
COVID-19 vaccine*	5582	7536	13118
Other vaccines**	149	1164	1313
Total	5731	8700	14431
*Menstrual disorders events reported after exposure to COVID-19 vaccine			
** Menstrual disorders events reported after exposure to other vaccines			
ROR = 5.78,(95%CI:4.86–6.88)			

Table 6  
Sensitivity analyses<sup>3</sup> (Distribution of adverse events stratified by age and vaccination status after exclusion of unknown age)

	<b>30–49 ages</b>	<b>Other ages</b>	<b>Total</b>
COVID-19 vaccine*	5582	2586	8168
Other vaccines**	149	860	1009
Total	5731	3446	9177
*Menstrual disorders events reported after exposure to COVID-19 vaccine			
** Menstrual disorders events reported after exposure to other vaccines			
ROR = 12.46,(95%C:10.41–14.92)			

## Discussion

Coronavirus disease 2019 (COVID-19) is as an emerging infectious disease (EID) that has caused the worst public health catastrophe of the 21st century thus far. In order to contain the spread of the epidemic, countries around the world have launched vaccination campaigns for COVID-19 vaccine and have taken various measures to monitor for adverse reactions after vaccination. VAERS as a vaccine adverse reaction self-reporting system, a total of 14,431 menstrual disorder-like events were reported by female in VAERS, and 13,118 (90.90%) were exposed to the COVID-19 vaccine, from the establishment of the database in 1990 to November 12, 2021. The general characteristics of the reports showed that female in the age group 30–49 years reported the highest number of incidents of menstrual disorders compared to other vaccines. There were 1065 reports mentioning serious adverse events, again with the highest percentage of reports for Pfizer-Biontech vaccination. The majority of reports of menstrual

disorders occurred after the first dose of the COVID-19 vaccine, with only about 0.5% reported after the third dose of the vaccine. The time between vaccination and adverse reaction reporting was within 100 days in 82.92% of patients, but only 18.01% of patients reported that their adverse reactions had disappeared, and 62.88% of patients reported that they still had adverse reactions related to vaccination.

To my knowledge, this is the first time that a menstrual disorder-related event has been linked to the COVID-19 vaccine. Normal female menstruation is judged by the cycle of menstruation, the period, the volume, the color, the quality and the accompanying symptoms of menstruation. Among the events of menstrual disorders reported by the COVID-19 vaccine, Menstruation irregular was found to be the most frequently reported, followed by Menstruation prolonged, Intermenstrual bleeding and Menstrual disorder, with Menorrhagia being the least frequently reported. Dietary nutrition, environmental factors, lifestyle and mental health conditions are important factors affecting menstrual irregularities in female of reproductive age<sup>[21]</sup>. During the covid-19 epidemic, female were more vulnerable to stress and were significantly more depressed and distressed than men<sup>[22]</sup>, and middle-aged females are the major groups for the first vaccination. This may explain the climb in reports of menstrual disorders after vaccination with the COVID-19 vaccine. Our study found a potential association signal between COVID-19 vaccine and menstrual disorders events with ROR = 7.83 and met the lower limit of ROR 95% CI > 1 and number of cases > 3. However, adverse reactions were reported independent of region, with ROR < 1. In addition, studies<sup>[23]</sup> have found a greater correlation between prolonged and irregular menstrual cycles and the risk of premature death (age < 70 years), so that menstrual disorders in female must be taken seriously enough.

Study shows age and gender differences in adults who report adverse reactions after vaccination with COVID-19 vaccine. However, after the launch of COVID-19 vaccine, attention to adverse reactions associated with vaccination has been focused on the elderly<sup>[8]</sup>, adolescents<sup>[9]</sup>, and even pregnant female and young children<sup>[24]</sup>, while attention to young adult female has been lacking. However, female of reproductive age account for the majority of adverse reaction reports received by VAERS for menstrual disorders. Our study found that reports of adverse reactions to menstrual disorders in females aged 30–49 years increased nearly tenfold compared to the pre-marketing period of the vaccine. There was a danger signal between this age group of female compared to other age groups for menstrual disorders events after COVID-19 vaccination with a lower limit of the ROR 95% CI > 1. To address some limitations of the spontaneous data, such as missing data in the report, a sensitivity analysis was conducted to exclude age unknowns and produce similar results. Reports of menstrual disorder-like events after vaccination of female with the COVID-19 vaccine are age-related, and females of reproductive age between 30–49 years old need to pay particular attention to adverse reactions after vaccination.

Three COVID-19 vaccines are authorized or approved for use among adults in the United States, respectively: mRNA-1273 from Moderna<sup>[5]</sup> BNT162b2 from Pfizer-BioNTech<sup>[4]</sup> Ad26.COV2 from Janssen<sup>[6]</sup>. Inoculation with Pfizer-BioNTech accounted for the majority of reports of menstrual disorders, with Moderna in second place and Janssen in third. As of November 2, 2021, approximately 248 million

doses of the Pfizer-BioNTech COVID-19 vaccine had been administered to persons aged  $\geq 12$  years in the United States<sup>[25]</sup>. And as of November 12, 2021, VAERS has received reports of menstrual disorders representing approximately 1 in 100,000 of the total number of Pfizer vaccinations. Adverse reactions to vaccination appear to be insignificant compared to the serious life-threatening effects of infection with the virus, and there is a lack of much substantial evidence linking vaccination to adverse reactions<sup>[26, 27]</sup>. Eric Wan and colleagues in *The Lancet Infectious Diseases* had suggested that the overall increased risk of Bell's palsy after COVID-19 vaccination. However, to this date there is no clear evidence of a link between the COVID-19 vaccine and Bell's palsy<sup>[28]</sup>. Based on various studies of real-world data<sup>[29, 30]</sup>, all approved or licensed COVID-19 vaccines provide substantial protection, although the degree of protection varies among vaccines.

However, there are several limitations to our study. First, the main limitation of our study is that it is unclear whether these adverse reactions were caused by disease or exposure to the vaccine, and there is a lack of data related to specific medical history and menstrual histories. Second, based on the spontaneous reporting nature of VAERS, our results are susceptible to various biases, such as data omission, overreporting, and underreporting. Third, co-vaccination may suppress or enhance the immune response, and this study only refers to the report of vaccination alone and does not include the data of co-vaccination. All of the above may cause bias in our results.

## Conclusion

From the signal detection results, there was a statistically significant association between COVID-19 vaccine and reports of adverse reactions to menstrual disorders, and COVID-19 may contribute to menstrual disorders in young adult female (30–49 years). However, our study data are from VAERS and the results may be influenced by the number and quality of reports, so it is challenging to study menstrual disorders directly defined as COVID-19 vaccine adverse events and should continue to track adverse reactions to vaccine in female in this age group.

## Declarations

### Ethics approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations.

### Availability of data and materials

We sincerely thank the VAERS for providing research data. This data can be found at: <https://vaers.hhs.gov/>.

### Competing interests

Author Bing Zhang, Author Xiao Yu, Author Jinxing Liu and Author Pengfei Liu declare that they have no conflict of interest.

## Funding

This study was supported by the Natural Science Foundation of Shandong Province, China (Grant No.: ZR2019PH053).

## Author contributions

Bing Zhang proposed the idea, and Xiao Yu participated in collecting VAERS data, performed data analysis, and wrote the first manuscript. Jinxing Liu and Pengfei Liu participated in the scientific discussions and manuscript writing, and made suggestions to improve the first manuscript. All authors have read and agreed to the published version of the manuscript.

## Authors' information

1. Bing Zhang Ph.D. in Chinese Gynecology, First School of Clinical Medicine, Shandong University of Traditional Chinese Medicine Shandong China;

2. Xiao Yu Ph.D. in Chinese Gynecology, Department of Gynecology Affiliated Hospital of Shandong University of Traditional Chinese Medicine Shandong China;

3. Jinxing Liu Professor; Department of Gynecology Affiliated Hospital of Shandong University of Traditional Chinese Medicine Shandong China;

4. Pengfei Liu: Lecturer; Department of Reproduction and Genetics, Affiliated Hospital of Shandong University of Traditional Chinese Medicine Shandong China;

## Consent for Publication

Not applicable.

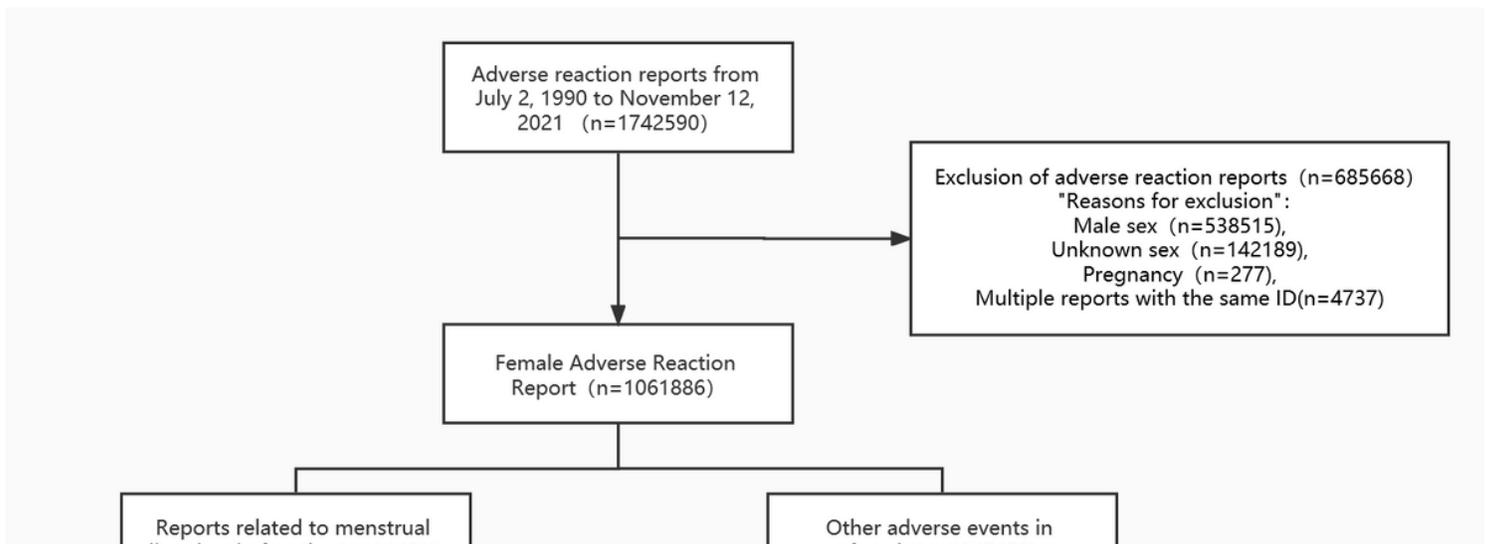
## References

1. Kevadiya B D, Machhi J, Herskovitz J, et al. Diagnostics for SARS-CoV-2 infections. [J]. Nature materials, 2021,20(5):593–605.
2. Singh J A, Upshur R E G. The granting of emergency use designation to COVID-19 candidate vaccines: implications for COVID-19 vaccine trials. [J]. The Lancet. Infectious diseases, 2021,21(4):e103-e109.
3. Coccia M. Optimal levels of vaccination to reduce COVID-19 infected individuals and deaths: A global analysis. [J]. Environmental research, 2022,204(Pt C):112314.

4. Oliver S E, Gargano J W, Marin M, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine - United States, December 2020. [J]. MMWR. Morbidity and mortality weekly report, 2020,69(50):1922–1924.
5. Oliver S E, Gargano J W, Marin M, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Moderna COVID-19 Vaccine - United States, December 2020. [J]. MMWR. Morbidity and mortality weekly report, 2021,69(5152):1653–1656.
6. Oliver S E, Gargano J W, Scobie H, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Janssen COVID-19 Vaccine - United States, February 2021. [J]. MMWR. Morbidity and mortality weekly report, 2021,70(9):329–332.
7. Moro P L, McNeil M M. Successes of the CDC monitoring systems in evaluating post-authorization safety of COVID-19 vaccines. [Z]. 20221–4.
8. Soiza R L, Scicluna C, Thomson E C. Efficacy and safety of COVID-19 vaccines in older people. [J]. Age and ageing, 2021,50(2):279–283.
9. Hause A M, Gee J, Baggs J, et al. COVID-19 Vaccine Safety in Adolescents Aged 12–17 Years - United States, December 14, 2020-July 16, 2021. [J]. MMWR. Morbidity and mortality weekly report, 2021,70(31):1053–1058.
10. Lin C. BNT162b2 Covid-19 Vaccine in Adolescents. [Z]. 2021: 385, 1342–1343.
11. Girardi G, Bremer A A. Scientific Evidence Supporting Coronavirus Disease 2019 (COVID-19) Vaccine Efficacy and Safety in People Planning to Conceive or Who Are Pregnant or Lactating. [J]. Obstetrics and gynecology, 2022,139(1):3–8.
12. Yang Y J, Murphy E A, Singh S, et al. Association of Gestational Age at Coronavirus Disease 2019 (COVID-19) Vaccination, History of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection, and a Vaccine Booster Dose With Maternal and Umbilical Cord Antibody Levels at Delivery. [J]. Obstetrics and gynecology, 2021.
13. Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. [J]. JAMA, 2021,325(8):780–781.
14. Bilotta C, Perrone G, Adelfio V, et al. COVID-19 Vaccine-Related Thrombosis: A Systematic Review and Exploratory Analysis. [Z]. 2021: 12, 729251.
15. Shimabukuro T T, Nguyen M, Martin D, et al. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). [J]. Vaccine, 2015,33(36):4398–4405.
16. Brown E G, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). [J]. Drug safety, 1999,20(2):109–117.
17. U.S. Food and Drug Administration. CFR-Code of Federal Regulations Title 21. U.S. Department of Health and Human Services [EB/OL].[2022-1-9].  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.80>.
18. Centers for Disease Control and Prevention. VAERS - Data Sets. U.S. Department of Health and Human Services [EB/OL]. [2022-1-10]. <https://vaers.hhs.gov/data/datasets.html?>

19. Rothman K J, Lanes S, Sacks S T. The reporting odds ratio and its advantages over the proportional reporting ratio. [J]. *Pharmacoepidemiology and drug safety*, 2004,13(8):519–523.
20. U.S. Department of Health & Human Services. Exemptions (2018 Requirements). Office for Human Research Protections [EB/OL]. [2022-1-9]. <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-a-46104/index.html>.
21. Nabolsi M, Safadi R, Sun C, et al. The health-related quality of life of Syrian refugee women in their reproductive age. [J]. *PeerJ*, 2020,8:e9990.
22. Petzold M B, Bendau A, Plag J, et al. Risk, resilience, psychological distress, and anxiety at the beginning of the COVID-19 pandemic in Germany. [J]. *Brain and behavior*, 2020,10(9):e1745.
23. Wang Y, Arvizu M, Rich-Edwards J W, et al. Menstrual cycle regularity and length across the reproductive lifespan and risk of premature mortality: prospective cohort study. [J]. *BMJ (Clinical research ed.)*, 2020,371:m3464.
24. Luxi N, Giovanazzi A, Capuano A, et al. COVID-19 Vaccination in Pregnancy, Paediatrics, Immunocompromised Patients, and Persons with History of Allergy or Prior SARS-CoV-2 Infection: Overview of Current Recommendations and Pre- and Post-Marketing Evidence for Vaccine Efficacy and Safety. [J]. *Drug safety*, 2021,44(12):1247–1269.
25. Woodworth K R, Moulia D, Collins J P, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5–11 Years - United States, November 2021[J]. *MMWR. Morbidity and mortality weekly report*, 2021,70(45):1579–1583.
26. Grubaugh N D, Cobey S. Of variants and vaccines. [Z]. 2021: 184, 6222–6223.
27. Fan G, Tu C, Zhou F, et al. Comparison of severity scores for COVID-19 patients with pneumonia: a retrospective study. [Z]. 2020: 56.
28. Cirillo N, Doan R. The association between COVID-19 vaccination and Bell's palsy. [J]. *The Lancet. Infectious diseases*, 2022,22(1):5–6.
29. Baden L R, El Sahly H M, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. [Z]. 2021: 384, 403–416.
30. Self W H, Tenforde M W, Rhoads J P, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions - United States, March-August 2021. [J]. *MMWR. Morbidity and mortality weekly report*, 2021,70(38):1337–1343.

## Figures



**Figure 1**

Flow diagram of case inclusion in this study