

VSD Menstrual Irregularities Working Group (MI-WG) protocol
Evaluation of possible association between COVID-19 vaccination and abnormal uterine bleeding

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Version Date: January 27, 2022

Background

Reports of menstrual irregularities following COVID-19 vaccine have been increasing, especially on social media platforms and in the Vaccine Adverse Event Reporting System.¹ These reports led the National Institutes of Health (NIH) to release a Notice of Special Interest for investigating these claims.² While there are a handful of publications around menstrual changes and COVID-19 *infection*, the conclusions range from “women should be reassured that SARS-CoV-2 has no impact on abnormal uterine bleeding (AUB) of any type including the symptoms of heavy and/or irregular menstrual bleeding” to “patients had various extents of transient menstrual changes, mainly manifesting as prolonged cycles and decreased volume.”^{3,4} However, one study found 16% of female or non-binary patients with COVID-19 infection reported changes in menstruation, which correlated with a greater number of COVID-19 symptoms.⁵

Little is known about how widespread menstrual irregularities are post COVID-19 *vaccination*, although it is an active area of investigation. One of the studies funded under the NIH mechanism described above found that COVID-19 vaccination is associated with a very small change in the length between cycles (less than one day), but not length of menses.⁶ A survey conducted by researchers at the University of Illinois at Urbana-Champaign is collecting self-reported data on menstrual changes after COVID-19 vaccination. While data collection and analysis is ongoing, to date the data are showing modest short-term menstrual changes.⁷ The United Kingdom’s Yellow Card reporting site received just over 37,000 reports of abnormal menstrual bleeding after vaccination as of January 2022, but given the common nature of menstrual irregularities, the Medicines and Healthcare products Regulatory Agency determined the data “does not support a link between changes to menstrual periods and related symptoms and COVID-19 vaccines.”⁸

There are currently sparse data available about people who present for medical care for abnormal uterine bleeding following COVID-19 vaccination, especially among specific sub-groups, including post-menopausal people. While there is some biological plausibility for post-vaccination bleeding in people with menstrual cycles,⁹ the same does not hold true for people who are post-menopausal since the cyclical hormonal and uterine changes are no longer occurring.¹⁰ The proposed study will investigate a range of abnormal uterine bleeding (AUB) diagnoses following covid-19 vaccination.

Study Objective

Provide a descriptive analysis of people with AUB medical diagnoses, including those who received a diagnosis within 60 days of COVID-19 vaccination.

Study Aims

Aim 1: In patients aged 16-64, calculate rates of AUB ICD-10 codes given between January 1, 2018, and October 31, 2021. Rates will be calculated by age group (16-24; 25-39; 40-54; 55-64 years), by month, over the study period.

Aim 2: Quantify and describe the population with AUB ICD-10 codes in the 60 days following receipt of COVID-19 vaccines administered from December 14, 2020, through latest month allowing full follow up (60 days post vaccination + 90 days).

Aim 3: To determine if the abnormal uterine bleeding could be related to the COVID-19 vaccination, chart review an age-stratified sample of medical records from patients identified in Aim 2. Records will be sampled from each of the pre-defined uterine bleeding ICD-10 codes.

Note: All three study aims will initially be performed at a single site (KPNW). Following completion of the analysis and discussion by the Menstrual Irregularities and/or Pregnancy working groups, the protocol may then be revised to allow for expansion to other VSD sites.

Methods

Aim 1 (incidence)

We propose to identify all Kaiser Permanente Northwest (KPNW) members aged 16-64 with abnormal uterine bleeding ICD-10 diagnosis codes in any setting administered between January 1, 2018, and December 31, 2021. We will present rates of AUB by month, by age group (16-24; 25-39; 40-54; 55-64 years). Age groups within the 16–64-year study population may be revised with input from the MI workgroup. [\[See table shells\]](#)

Monthly rates will be calculated using the number of patients meeting the inclusion and exclusion criteria below as a denominator, and the number with any of the pre-specified diagnosis codes as the numerator. Rates will be calculated in person-days for each month of analysis. Age will be determined as of the first of the month of analysis. Due to age progression, patients in the denominator may span two age groups over the study period. Patients will be censored at the first occurrence of a code of interest and will not contribute to the denominator in the 24 subsequent months, as per the exclusion criteria below.

Rates from the data collection tables below will be graphed when available.

Data Collection Table 1. Monthly AUB incidence – **total population**

Month of analysis	Eligible members (n)	Members with ≥ 1 AUB code (n)	Rate of AUB diagnosis (Per 1000 person-days)
(Rows for 1/2018 through 10/2021)			

Data Collection Table 2. Monthly AUB incidence – **Ages 16-24**

Month of analysis	Eligible members (n)	Members with ≥1 AUB code (n)	Rate of AUB diagnosis (Per 1000 person-days)
(Rows for 1/2018 through 10/2021)			

Data Collection Table 3. Monthly AUB incidence – **Ages 25-39**

Month of analysis	Eligible members (n)	Members with ≥1 AUB code (n)	Rate of AUB diagnosis (Per 1000 person-days)
(Rows for 1/2018 through 10/2021)			

Data Collection Table 4. Monthly AUB incidence – **Ages 40-54**

Month of analysis	Eligible members (n)	Members with ≥1 AUB code (n)	Rate of AUB diagnosis (Per 1000 person-days)
(Rows for 1/2018 through 10/2021)			

Data Collection Table 5. Monthly AUB incidence – **Ages 55-64**

Month of analysis	Eligible members (n)	Members with ≥1 AUB code (n)	Rate of AUB diagnosis (Per 1000 person-days)
(Rows for 1/2018 through 10/2021)			

We will also provide the prevalence of AUB in the study population (the number of unique patients with at least one AUB code during the study period [patients with a diagnosis/total unique patients]). We will provide descriptive statistics for those in the population with at least one AUB diagnosis code, including basic demographics (age and race/ethnicity) and the number of AUB codes per patient over the study period.

As a secondary objective, to examine the healthcare burden caused by AUB over the Aim 1 period, we will calculate the prevalence of all AUB codes within the population, by month and age group, without censoring based on history of AUB diagnoses. We will calculate total AUB diagnoses each month, both overall and by pre-specified code; all AUB diagnosis codes given on the same day will be included.

Inclusion

Denominator:

- 1) Ages 16-64 as of the 1st of the month of analysis (Jan 2018 through December 2021)
 - a. Age-stratified analyses will be limited to those in the age groups of interest (see Data Collection Tables 2-4 above).

- 2) Active membership in any day of the month of analysis
- 3) Female sex in EMR

Numerator:

- 1) Of those in the denominator, limited to those who have ≥ 1 of the following ICD-10 codes in the month of analysis.

Excessive, frequent and irregular menstruation

- [N92.0](#) Excessive and frequent menstruation with regular cycle
- [N92.1](#) Excessive and frequent menstruation with irregular cycle
- [N92.3](#) Ovulation bleeding
- [N92.4](#) Excessive bleeding in the premenopausal period
- [N92.5](#) Other specified irregular menstruation
- [N92.6](#) Irregular menstruation, unspecified

[N93.8](#) Other specified abnormal uterine and vaginal bleeding

[N93.9](#) Abnormal uterine and vaginal bleeding, unspecified

[N95.0](#) Postmenopausal bleeding

Exclusion

- 1) ≥ 1 of the following ICD-10 codes in the medical record in the two years prior to the month of analysis

Excessive, frequent and irregular menstruation

- [N92.0](#) Excessive and frequent menstruation with regular cycle
- [N92.1](#) Excessive and frequent menstruation with irregular cycle
- [N92.3](#) Ovulation bleeding
- [N92.4](#) Excessive bleeding in the premenopausal period
- [N92.5](#) Other specified irregular menstruation
- [N92.6](#) Irregular menstruation, unspecified
- [N93.8](#) Other specified abnormal uterine and vaginal bleeding
- [N93.9](#) Abnormal uterine and vaginal bleeding, unspecified
- [N95.0](#) Postmenopausal bleeding

- 2) Any of the following diagnoses:

a. At any time

- i. Ehlers-Danlos syndrome (Q79.60-63, Q79.69)
- ii. Other coagulation effects (D68.XXX)
- iii. Thalassemia (D56.X)
- iv. Sickle cell disease (D57.XXX)
- v. Organ transplant (Z94.XX, Z48.XXX)
- vi. Congenital and hereditary thrombocytopenia purpura (D69.42)

b. In the 3 months prior to the month of analysis:

- i. Cancer treatment (see [CANCER](#) codes)

- ii. Platelet dysfunction (D69.1)
 - iii. Thrombocytopenia (D69.3, D69.41, D69.49, D69.5X, D69.6, D69.8, D69.9)
 - iv. Dialysis (Z49.XX, Z99.2, N18.6)
 - v. Anticoagulation therapies (Z79.01, Z79.02, Z79.899)
 - vi. End stage liver disease/Cirrhosis (K70.3X, K71.7, K74.3-6X, P78.81, E83.110, B19.10, B19.20)
- 3) Any pregnancy episode in the 90 days prior to and including the month of analysis (e.g., members with pregnancy episodes in any of the March-April-May-June period would be excluded from June analyses)
 - 4) History of total hysterectomy (Z90.710)

Aims 2 and 3 (post-vaccination bleeding)

We propose to identify all patients at KPNW with new abnormal uterine bleeding in the 60 days following receipt of a COVID-19 vaccine, using ICD-10 diagnosis codes.

Inclusion

- 1) Receipt of a COVID-19 vaccine (any formulation, any dose) between 12/14/2020 and the latest month allowing full follow up (60 days post vaccination + 90 days).
- 2) ≥ 1 of the following ICD-10 codes in the 60 days following a COVID-19 vaccination (exclude day 0 of vaccination), in any setting

Excessive, frequent and irregular menstruation

[N92.0](#) Excessive and frequent menstruation with regular cycle

[N92.1](#) Excessive and frequent menstruation with irregular cycle

[N92.3](#) Ovulation bleeding

[N92.4](#) Excessive bleeding in the premenopausal period

[N92.5](#) Other specified irregular menstruation

[N92.6](#) Irregular menstruation, unspecified

[N93.8](#) Other specified abnormal uterine and vaginal bleeding

[N93.9](#) Abnormal uterine and vaginal bleeding, unspecified

[N95.0](#) Postmenopausal bleeding

- 3) ≥ 2 years of continuous enrollment as of date of AUB code
- 4) ≥ 90 days of follow-up (enrollment) after AUB code
- 5) 16-64 years of age at time of AUB code

Exclusion

- 1) ≥ 1 of the following ICD-10 codes in the 2 years prior to the index date (date of initial AUB code following vaccination)

Excessive, frequent and irregular menstruation

- [N92.0](#) Excessive and frequent menstruation with regular cycle
- [N92.1](#) Excessive and frequent menstruation with irregular cycle
- [N92.3](#) Ovulation bleeding
- [N92.4](#) Excessive bleeding in the premenopausal period
- [N92.5](#) Other specified irregular menstruation
- [N92.6](#) Irregular menstruation, unspecified
- [N93.8](#) Other specified abnormal uterine and vaginal bleeding
- [N93.9](#) Abnormal uterine and vaginal bleeding, unspecified
- [N95.0](#) Postmenopausal bleeding

2) Any of the following diagnoses:

- a. At any time
 - i. Ehlers-Danlos syndrome (Q79.60-63, Q79.69)
 - ii. Other coagulation effects (D68.XXX)
 - iii. Thalassemia (D56.X)
 - iv. Sickle cell disease (D57.XXX)
 - v. Organ transplant (Z94.XX, Z48.XXX)
 - vi. Congenital and hereditary thrombocytopenia purpura (D69.42)

- b. In the 3 months prior to the index date:
 - i. Cancer treatment (see [CANCER](#) codes)
 - ii. Platelet dysfunction (D69.1)
 - iii. Thrombocytopenia (D69.3, D69.41, D69.49, D69.5X, D69.6, D69.8, D69.9)
 - iv. Dialysis (Z49.XX, Z99.2, N18.6)
 - v. Anticoagulation therapies (Z79.01, Z79.02, Z79.899)
 - vi. End stage liver disease/Cirrhosis (K70.3X, K71.7, K74.3-6X, P78.81, E83.110, B19.10, B19.20)

3) Any pregnancy episode in the 90 days prior to index date

4) History of total hysterectomy (Z90.710)

Planned descriptive statistics of covid-19 vaccinated patients with AUB

Overall descriptive statistics:

- 1) Number of patients with ≥ 1 AUB diagnosis codes in the 60 days post COVID-19 vaccination (after any dose)
 - a. Of those identified in #1, number with an AUB code in an inpatient setting (any of the AUB codes of interest, within the 60-day window – not limited to initial code)
 - b. Of those identified in #1, number with an AUB code in the ED setting (any of the AUB codes of interest, within the 60-day window – not limited to initial code)
- 2) Mean (SD), median (range) number of AUB codes per patient in the 60 days post any COVID-19 vaccination (all AUB codes, even if non-unique)

- 3) Mean (SD), median (range) number of **days** with ≥ 1 AUB code per patient in the 60 days post any COVID-19 vaccination (any AUB code)

Table 1 (extracted from EMR): **Demographic and clinical characteristics of individuals with AUB diagnoses following COVID-19 vaccination**

Limited to first bleeding code (unique patients)	N (%)	Chart review sample N (%)
Initial bleeding code N92 Excessive, frequent and irregular menstruation N92.0 Excessive and frequent menstruation with regular cycle N92.1 Excessive and frequent menstruation with irregular cycle N92.3 Ovulation bleeding N92.4 Excessive bleeding in the premenopausal period N92.5 Other specified irregular menstruation N92.6 Irregular menstruation, unspecified N93.8 Other specified abnormal uterine and vaginal bleeding N93.9 Abnormal uterine and vaginal bleeding, unspecified N95.0 Postmenopausal bleeding		
Encounter setting of initial code Email Phone/Virtual Outpatient Urgent care Emergency department Inpatient		
Age at time of first bleeding code (mean, range) 16-24 years 25-39 years 40-54 years 55-64 years		
Hispanic Yes No Unknown		
Race Non-Hispanic White Black Other Unknown		
Vaccine product closest to initial bleeding code Pfizer Moderna J&J/Janssen		
Number of doses received prior to initial bleeding code 1		

2		
3		
≥4		
Days from vaccine administration* to first bleeding code (mean, SD)		
Medical treatment received		
Iron infusion		
IV fluids		
D&C		

*Dose preceding bleeding code

A chart abstraction form has been developed and pilot tested at KPNW. Of the patients identified in Aim 2, we will review a subset of cases to determine how many of the patients identified have abnormal bleeding that could be attributed to COVID vaccination (absence of other clinical diagnoses or overt attribution by a clinician). Elements to be abstracted are shown in Tables 2-5 below, plus medical treatment received in Table 1.

The population for chart review will be age-stratified (16-24; 25-39; 40-54; 55-64 years), and by pre-specified AUB ICD-10 code. Numbers for chart review will be determined after examination of total case numbers identified in Aim 2, and numbers within each stratum.

We will identify clinicians who have experience with menstrual irregularities in the MI-WG to help with refinement of the chart abstraction form, and adjudication of cases, as needed.

Clinical characteristics of chart reviewed AUB cases

Table 2: Chart reviewed AUB cases - Type of abnormal bleeding reported

	N (%)
Post-menopausal bleeding	
Breakthrough/spotting/intermenstrual	
Heavy bleeding	
Longer than typical bleeding	
Missed/late period	
Other irregular bleeding	

Table 3 - Chart reviewed AUB cases - Birth control use in the 60 days prior to index date

	Using as of index date N (%)	Stopped within 60 days of index date N (%)
No hormonal/copper IUD use		N/A
Oral contraceptive pills		
Hormonal IUD		
Copper IUD		
Implant (Nexplanon)		

Depo-Provera shot		
Patch		
Ring (NuvaRing or Annovera)		

Table 4 - Chart reviewed AUB cases - Diagnostic work-up to determine cause of bleeding

	N (%)	N (%) with abnormal finding related to bleeding
Office exam		
Bloodwork/Urine		
Ultrasound		
MRI		
Endometrial or other biopsy		
Other work-up		

Table 5: Outcome/bleeding cause (this will be described in the text)

	N (%)
Covid-19 vaccination	
Uterine lesions (fibroid/myoma/polyp):	
Cervical lesions	
Precancer (hyperplasia)/Cancer	
Ovarian cyst(s)	
PCOS / anovulatory cycle	
Endometriosis	
Medical procedure/surgery	
Infection	
Other	
Unknown cause	

Preliminary Data

As of November 22, 2021, **991** unique patients meeting inclusion and exclusion criteria described above (excluding item 2 in the exclusion criteria list) in the KPNW system received an AUB diagnosis code of interest in the 60 days following receipt of a COVID-19 vaccine (any dose). The mean number of codes received by patients in the 60 days following COVID-19 vaccination was 1.92 (range 1-14). Patients ranged in age from 18-64 years; 66% of patients received the initial bleeding code following a second dose of a COVID-19 vaccine. Mean days from vaccine administration to initial AUB code was 27 (SD 17), and the most common codes received were N93.9 Abnormal uterine and vaginal bleeding, unspecified (52%), N92.0 Excessive and frequent menstruation with regular cycle (15%), N95.0 Postmenopausal bleeding (9%), and N92.6 Irregular menstruation, unspecified (9%).

References

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- ¹⁰ [Can COVID-19 vaccines cause post-menopausal bleeding? Here's what we know - National | Globalnews.ca](https://www.globalnews.ca/news/covid-19-vaccines-cause-post-menopausal-bleeding-heres-what-we-know/)