

# Etiology Model for Elevated Histamine Levels Driving High Reactogenicity Vaccines (including COVID-19) Associated Menstrual Adverse Events

Darrell O. Ricke, Ph.D. (✉ [doricke@gmail.com](mailto:doricke@gmail.com))

<https://orcid.org/0000-0002-2842-2809>

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## Research Article

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# Abstract

**Introduction:** Some women are experiencing menstrual changes, including altered menstrual duration, volume (heavier bleeding), increased dysmenorrhea, and worsened premenstrual syndrome (PMS) following Coronavirus disease 2019 (COVID-19) spike vaccinations. Appreciation of these as temporal adverse events associated with COVID-19 spike vaccinations was slow to develop. The etiology of these menstrual adverse events associated with COVID-19 spike vaccination remains unknown.

**Methods:** The United States Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS) database was data mined for data reported adverse events affecting menstrual cycles by vaccine type.

**Hypothesis:** This article proposes the hypothesis that vaccinations can induce a temporary surge in histamine levels immediately post vaccination as part of the innate immune response. Increasing histamine levels is known to increase estrogen levels. Further, it is proposed that this temporary surge in histamine levels causes temporary Histamine Intolerance in some women and causes the menstrual adverse events temporally associated with vaccinations.

**Conclusion:** Prophylactic and therapeutic treatment of vaccinees with diamine oxidase and/or specific antihistamines may reduce the incidence rate and/or severity of menstrual adverse events associated with vaccines with high reactogenicity, including SARS-CoV-2 vaccines and boosters. This model predicts menstrual associated adverse events incidence levels correspond to vaccine reactogenicity.

## Introduction

Following reports (e.g., [1, 2]) that some women were experiencing adverse events unexpected vaginal bleeding/intermenstrual bleeding, changes to periods, heavy menstrual bleeding, missed menstruation, irregular menstruation, delayed menstruation, unusual menstrual discomfort, and painful periods (dysmenorrhoea) post COVID-19 spike vaccinations, the United States National Institutes of Health (NIH) funded studies to assess potential effects of COVID-19 vaccination on menstruation [3]. As of Dec. 1, 2021 the United Kingdom Medicines & Healthcare products Regulatory Agency (MHRA) Yellow Card system had 43,916 suspected reactions relating to a variety of menstrual disorders including heavier than usual periods, delayed periods, and unexpected vaginal bleeding [4]. Smoking and prior COVID-19 are factors for increased risk and oestradiol-containing contraceptives are a protective factor [5]. A retrospective study reports a small change in menstrual cycle length but not menses length following COVID-19 vaccination [6]. Another survey found increased menstrual disturbances post COVID-19 vaccination [7]; women who had experienced increased heavy bleeding after first vaccine dose had a high risk of having the same experience after the second dose (63.4%) [7]. Any connection between COVID-19 spike vaccinations and disruption of menstrual cycles is unknown.

The innate immune system responds immediately to vaccinations. Activation of granulocytes and mast cells that release inflammatory molecules including histamine is part of the normal immune response.

Histamine exerts its effects primarily by binding to G protein-coupled histamine receptors, designated H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub>, and H<sub>4</sub> (reviewed[8]). Individuals have a threshold over which elevated histamine levels trigger Histamine Intolerance (HIT) syndrome. Drugs[9], foods (cocoa, spinach, tomatoes, beer, wine, cheeses, meat, soy, yogurt, fermented foods, etc.[9, 10]), gastrointestinal microbiome[9], and stage of menstrual cycle (7) all affect an individual's histamine tolerance/intolerance threshold. Histamine is inactivated by diamine oxidase (DAO) or Histamine N4-methyltransferase (HNMT). DAO is expressed in liver hepatocytes, kidney proximal tubular cells[11, 12], digestive tract, and placenta. HNMT is expressed in multiple cell types (8, 9). DAO and HNMT alleles and expression levels may affect rates of histamine metabolism (10, 11). Low serum DAO activity is associated with histamine intolerance[15, 16]. Increases in histamine levels are known to elevated estrogen levels[17] and may play a role in dysmenorrhea (15).

## Working Hypothesis

This article proposes the hypothesis that elevated histamine levels, from innate immune system response to vaccination, cause the menstrual adverse events temporally associated with vaccinations experienced by some female vaccinees. This model predicts incidence levels of these menstrual adverse events correlate with vaccine reactogenicity.

## Methods

The Vaccine Adverse Event Reporting System (VAERS) database[19] was data mined for data on reported adverse events affecting menstrual cycles by vaccine type. Adverse event reports of dysmenorrhoea, heavy menstrual bleeding, intermenstrual bleeding, menstrual discomfort, menstrual disorder, menstruation delayed, menstruation irregular, premenstrual syndrome, and premenstrual pain were extracted. The downloaded data include all adverse events reported from 1990 to November 19, 2021. A Ruby program named `vaers_slice.rb` was developed to tally selected reported vaccine adverse events by vaccine and day of onset. Microsoft Excel was used create Fig. 1.

## Results

The majority of all menstrual adverse events in VAERS from 1990 to November 19, 2021 are summarized in Table 1. The three vaccines with the largest number of reported adverse events are shown for each reported adverse event description; these vaccines are COVID-19 spike vaccines, and two human papillomavirus (HPV) vaccines (Gardasil and Cervarix). The COVID-19 adverse events ranged from 93.9% for "Menstration irregular" across all vaccines to as high as 99.6% for both "Heavy menstrual bleeding" and "Intermenstrual bleeding". The majority of the reported COVID-19 menstrual adverse events reports have immediate onset (Fig. 1) for all doses of Moderna mRNA-1273, Pfizer/BioNTech BNT162b2, and Janssen Ad26.COV2-S spike vaccines.

Table 1

VAERS Menstrual symptoms for COVID-19 (Pfizer/BioNTech BNT162b2, Moderna mRNA-1273, and Janssen AD26.COVS-2), human papillomavirus vaccines (Gardasil and Cervarix), and all VAERS vaccines reported from 1990 to November 19, 2021.

VAERS Symptom	COVID19	HPV (Gardasil)	HPV (Cervarix)	All Vaccines	% COVID19
Heavy menstrual bleeding	9,456	6		9,539	99.1%
Menstruation irregular	5,467	258	118	6,018	90.8%
Dysmenorrhoea	5,032	157	97	5,395	93.3%
Menstrual disorder	4,215	185	65	4,633	91.0%
Menstruation delayed	3,115	106	4	3,281	94.9%
Intermenstrual bleeding	2,489			2,510	99.2%
Premenstrual syndrome	319	4	2	331	96.4%
Premenstrual pain	166			169	98.2%
Menstrual discomfort	82	2	1	88	93.2%
Menstrual total	30,341	718	287	31,964	94.9%

## Discussion

Histamine is known to play a role in the menstrual cycle[10]. This article advances the hypothesis that elevated histamine levels, inducing temporary Histamine Intolerance, causes reported impacts on the menstrual cycle for some women within days post vaccination. Figure 1 shows that the majority of the reported adverse events coincide in time when the histamine levels are predicted to be elevated (i.e., immediately following COVID-19 spike vaccination). The number of these reported menstrual adverse events associated with COVID-19 spike vaccinations significantly exceeds that of all other vaccines reported since 1990, see Table 1. This imbalance is also observed for other COVID-19 spike vaccine adverse events[20]. Histamine may be the cause of dysmenorrhea (menstrual pain) associated with decreases in DAO levels at the start of menstruation[21].

Support for the hypothesis that vaccines are inducing elevated histamine levels in affected women can be obtained by measuring histamine and metabolite levels before and after vaccination in clinical studies.

### Candidate Treatments Suggested by Elevated Histamine Model

Evaluation of candidate treatments with the potential to lessen or reduce the number of adverse events can be obtained from case series, and cohort studies of candidate antihistamines and/or DAO treatment prophylactically prior to and post COVID-19 spike vaccination or booster vaccination. Treatment

duration could be aligned with observed duration of elevated histamine levels with a predicted treatment course of several days. These clinical results could support the justification for randomized clinical trial(s) of these candidate treatments. For COVID-19 patients, specific H<sub>1</sub> and H<sub>2</sub> antihistamines are showing efficacy with doses aligned with targeting immune cells[22,23]. DAO and these antihistamines and dosages are potential candidates for initial evaluations: cetirizine (H<sub>1</sub>) [24,25], dexchlorpheniramine (H<sub>1</sub>) (21), and high dose famotidine (H<sub>2</sub>)[22,26].

## Summary

Some women are experiencing menstrual adverse events post COVID-19 spike vaccination. Herein, this article proposes that these vaccines associated adverse events, occurring within days of vaccination, are caused by elevated histamine levels from immediate innate immune responses to high reactogenicity vaccines. This hypothesis suggests concurrent treatment with specific antihistamines and/or DAO for several days may lower the incidence rate, reduce severity, or adverse event duration post vaccination with COVID-19 spike vaccines, COVID-19 boosters, and other vaccines with higher reactogenicity.

## Declarations

### Consent statement/Ethical approval

Not required

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None.

### Declaration of interests

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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### Authorship

The author attest they meet the ICMJE criteria for authorship.

## Abbreviations

COVID-19    Coronavirus disease 19

DAO            diamine oxidase

HIT	Histamine Intolerance
HPV	Human papillomavirus
HNMT	Histamine N4-methyltransferase
MHRA	Medicines & Healthcare products Regulatory Agency
NIH	National Institutes of Health
PMS	premenstrual syndrome
VAERS	Vaccine Adverse Event Reporting System

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## Figures

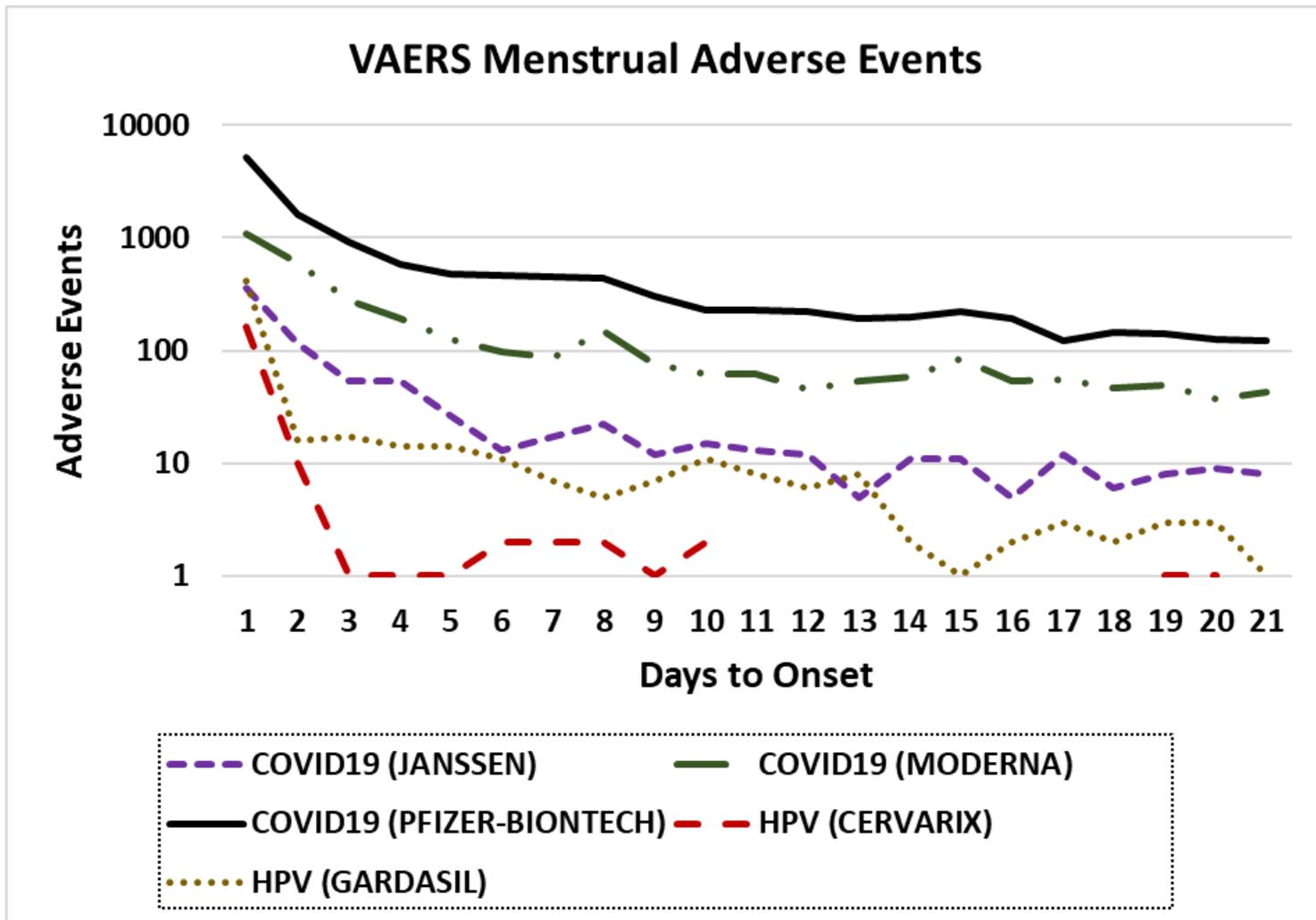


Figure 1

Menstrual adverse events post COVID-19 vaccination by vaccine (Pfizer/BioNTech BNT162b2, Moderna mRNA-1273, Janssen AD26.CO2-S, HPV Gardasil and Cervarix) and day of onset (Y-axis shown with log<sub>10</sub> scale). Top five vaccines with VAERS menstrual adverse events reported from 1990 to November 19, 2021 include Dysmenorrhoea, Heavy menstrual bleeding, intermenstrual bleeding, menstruation delayed, menstruation irregular, premenstrual syndrome, and premenstrual pain.

## Supplementary Files

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- [Allmenstrual.xlsx](#)
- [Menstrual.xlsx](#)