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► **To cite this version:**

Alexandra Alvergne. Why we must fight ignorance about COVID-19 vaccines and menstrual cycles. Trends in Molecular Medicine, 2023, 10.1016/j.molmed.2023.06.005 . hal-04156989

**HAL Id: hal-04156989**

**<https://hal.umontpellier.fr/hal-04156989v1>**

Submitted on 16 Nov 2023

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## Science &amp; Society

## Why we must fight ignorance about COVID-19 vaccines and menstrual cycles

Alexandra Alvergne <sup>1,\*</sup>

**The COVID-19 pandemic has revealed a critical gap in female health science, fueling anxiety, polarized views, and vaccine hesitancy. Although menstrual cycles feel like a niche topic for some, efforts to augment knowledge on the ‘fifth vital sign’ experienced by more than 300 million people on any given day worldwide are crucial to promote gender equity in health.**

### A dearth of research on vaccines and menstrual cycles

Who wants to hear about vaginal bleeding? Uneasy conversations around periods are common. More than one in three boys (37%) think periods should be kept a secret, and half think periods are dirty (55%), according to research by Plan International [1]. The topic of menstruation is tainted by ignorance and invisibility, due to deeply entrenched beliefs about menstrual pollution and associated taboos about what women can and cannot do on menstrual bleeding days. Taboos lead to stigmas, the social exclusion of people, and prevent open, not to mention scientific discussion, around menstruation.

Given this, it is not surprising that before the pandemic struck, only a handful of studies were published on menstrual cycles and vaccines [2]. Not a definition of a hot topic. Yet menstrual disturbances including changes in cycle length and/or heavy bleeding following vaccination had been reported as early as 1913 for the typhoid

vaccine in the USA. Subsequent research was only in 1982, when no association was found with the hepatitis vaccine among 27 employees of a Japanese factory, and then again in 2018, when mixed results were reported for the human papilloma vaccine, in Japan again. In addition to being sparse, evidence was noncausal, and various methodological issues including recall and selection biases, the absence of control, and the lack of systematic measures undermined the validity of the findings.

Yet menstrual health matters well beyond fertility issues: irregular periods associate with the risks of cardiovascular diseases, chronic diseases, and premature mortality [3], which is partly why menstruation has been coined the fifth vital sign [4]. Fortunately, the world is moving forward and, in this area, the pandemic has been a game changer. Testimonies of perceived menstrual side-effects following COVID-19 vaccination drastically increased public awareness to the topic, leading the scientific community to gather new data and do the research. Attention to COVID-19 vaccines and their potential impact on menstrual cycles has increased sixfold compared to other vaccines, with >30 articles published since 2020, including editorials [4], reviews [5], and research articles using large surveys and digital health data.

Three years in, what is the story so far? What are the vaccine side effects on the menstrual cycle? Are they common? Serious? Who is most at risk? What are the mechanisms? How can we be sure? Science is now talking; are we ready to listen?

### Potentially common but not clinically serious side effects

The story so far is that COVID-19 vaccination does not harm fertility [4] and is significantly associated with small and temporary changes in cycle length (from less than a day [6–8] to just over 2 days

[9]) and heavier bleeding (40 additional people per 1000 [10]). Those changes are temporary, most resume within one cycle, and overall, there are no data raising an alarm from a clinical perspective. Yet, it does not mean that menstrual changes do not occur or that they are not a problem. They do, and that needs to be acknowledged too.

People do report changes to their menstrual cycles following COVID-19 vaccination; mostly heavier but also lighter bleeding, longer and shorter cycle length, spotting, breakthrough bleeding, and increased premenstrual syndrome. It is tenuous to infer causality in the absence of an experimental design or a control group: changes may have been due to other reasons than vaccines, such as living conditions during the pandemic, which has been associated with changes in anovulatory cycles [11]. Despite those caveats, evidence from both cycle data prospectively collected [9] using mobile apps [6,7] and retrospectively collected data including a control group [12] do suggest the effect is real, albeit small and temporary. Although estimating the frequency of menstrual side effects is difficult because people who experience problems are more likely to take up a survey on this topic, one study using stratified sampling based on age and income estimate it to be about one in five people [12] – a potentially common side effect. For reference, pain at the injection site after the COVID-19 Pfizer vaccine is about one in ten people.

While many people experience menstrual cycle changes following COVID-19 vaccination, there is no cause for concern. In our recent research [12], the risk to report abnormal cycle parameters according to the International Federation of Gynecologist and Obstetricians (FIGO) was the same between unvaccinated and vaccinated groups, on average [12]. Studies using cycle data could not find an increased risk

to experience changes in cycle length >8 days [6]. Similarly, the Pharmacovigilance Risk assessment committee (PRAC) of the European Medicines Agency (EMA) found no link between mRNA COVID-19 vaccines and the absence of menstruation for  $\geq 90$  days; thus, no link with infertility. Ovarian reserve measured by plasma anti-Müllerian hormone (AMH) in a prospective sample of 129 women was not altered 3 months after mRNA COVID-19 vaccination, and the degree of immune response was not associated with AMH levels [13]. Note that a temporary drop in serum AMH after COVID-19 vaccination was found in another sample, but the decrease was transient and mostly reversible [14]. Overall, there are no studies to suggest that getting COVID-19 vaccination is putting menstrual health at risk.

### Data must prevail against polarization

Being able to tell people both yes, you might experience menstrual disturbances after vaccination, and no, there are no data so far to suggest it has any serious health or fertility consequence [12], seems like a helpful and important story to tell. Yet, it has been challenging to communicate this message efficiently to a broad audience, where the conversation gets pulled towards polarized views.

After my colleagues and I published that one in five people taken from a sample broadly representative of the UK reported experiencing changes to their menstrual cycles after vaccination, Sky News reported ‘COVID-19 vaccines do not affect a woman's menstrual cycle’; a statement that clearly misses the point: up to 20% of people experienced noticeable changes in this sample. Conversely, because we communicated that COVID-19 vaccines were okay for menstrual health, from a clinical perspective, I received a storm of chilling messages on social media (“How dare you? We hope justice will be served”, etc.). I believe this rather extravagant response results not only from the binary discourse

around vaccines (good vs bad), and the misunderstanding of epidemiological sciences, which report on population average rather than individual perspectives, it also results from dismissing menstrual side effects post-COVID-19 vaccines as real, just because they are not clinically significant. Unexpected bleeding changes can be a serious problem if you live in the street, if you are a schoolgirl with stained clothes, if you are trying to conceive, if you must work while experiencing crippling cramps or if you lack access to basic sanitation services at home. Especially if medical authorities did not warn you. In contrast, The American Society for Reproductive Medicine stated early in the pandemic that there was no biologically plausible mechanism by which the vaccine could affect fertility. A number have been proposed since then to explain links between vaccines and menstrual irregularities [4] (Box 1).

Women's health research has been on the back seat for too long. While the story around COVID-19 vaccines and menstruation becomes clearer every day, there is still much to be done to understand how to best administer vaccines to female bodies. There are questions for which we

do not have a good answer yet, and much to improve in our research designs (Box 2). Evidence-based knowledge on menstrual health is crucially needed to inform patient–doctor counseling and help people make an informed choice, thereby gaining increased control over their bodies. Although menstruation is being used as a trojan horse to promote vaccine hesitancy, this shall not deter the young science of menstrual health from pushing the research agenda forward.

### Who is most at risk?

In our study specifically investigating 33 risk factors in a large sample of participants living in the UK, we found that smokers, and those who had been infected with SARS-CoV-2 prior to receiving the vaccine, were at an increased risk to report changes [12]. We think those factors exacerbate the inflammation triggered by the COVID-19 vaccine, but replication is needed. In other studies, age also associates with an increased risk of heavier bleeding [15], suggesting issues related to endometrial repair [4]. There is no strong link between endometriosis, polycystic ovary syndrome (PCOS) [9,12] and post-COVID-19 menstrual changes, although

#### Box 1. What is the mechanism?

The brand of vaccines does not associate with the magnitude or type of menstrual cycle changes in most studies. Rather, menstrual cycle disturbances likely result from mounting an immune response to COVID-19 antigens. The pathways through which COVID-19 vaccination triggers changes in cycle length and bleeding may differ, as suggested by the low correlation between symptoms [12].

#### Cycle length

Due to energetic and functional trade-offs between immunity and reproduction [17], an immune challenge early in the cycle may lead to a delayed ovulation and an increase in cycle length [8]. An immune challenge may also activate stress-related glucocorticoids, leading to menstrual irregularities.

#### Heavy bleeding

ACE-2 receptors, the major cell entry receptors for SARS-CoV-2, are widely expressed in the ovarian follicles and the endometrium. ACE-2 receptors initiate the production of cytokines [proinflammatory cytokines interleukin (IL)-6, IL-8 and tumor necrosis factor  $\alpha$ ] that may increase myometrium contractility and lead to coagulation dysfunction [2].

#### Exogenous estradiol

The use of estrogen-based contraceptives decreases the risk to experience menstrual changes in at least two studies [9,12], possibly because of the potent immune response against viral infection afforded by exogenous estradiol, attenuating the development of a cytokine storm.

### Box 2. Guidance for improving menstrual health research

- Use international standards (FIGO) for cycle parameters
- Compare different inclusion criteria (e.g., with and without normal menstrual cycle parameters or disease at baseline)
- Use prospective designs whenever possible
- Include a control group
- Use random stratified sampling
- Include people with natural menstrual cycles in clinical trials
- Conduct studies among underprivileged groups
- Ask participants about their periods (FIGO criteria) in clinical trials
- Include menstrual cycle variables at enrolment and over time in cohorts and Biobanks
- Research what is the optimal timing of the menstrual cycle for vaccine efficacy
- Research what is the optimal timing of the menstrual cycle to reduce the adverse effects of the vaccine on menstruation

it depends on the sample [15]. Less is known about the influence of non-reproductive conditions including non-communicable diseases (diabetes or cardiovascular and autoimmune diseases),

Some researchers prefer using restricted inclusion criteria for methodological purposes, sampling people with normal cycles and without gynaecological disorders specifically, but others emphasize the needed to be more inclusive; both approaches are valid because humans live in diverse socioecologies and our sampling strategies should reflect that. We now have a better idea of the magnitude of changes in cycle frequency and bleeding post-COVID-19 vaccination in samples of individuals with normal cycles to begin with. Such samples are necessary if we want to demonstrate that associations are not caused by pre-existing health conditions. However, little is known about people living in harsh environmental conditions and/or with power relations that disadvantage them. Girls and women living in poverty, who might already be experiencing secondary amenorrhea due to stress and/or malnutrition, possibly suffer more intense or prolonged menstrual disturbances following the immune challenge brought about by vaccines. Establishing the impact of COVID-19 vaccines on the menstrual health of hard-to-reach populations who

may be less likely to take up an online survey or track their periods on their phones requires innovative strategies. The picture is not yet complete on who is most at risk.

However, the risk to experience menstrual cycle changes following vaccines should be balanced against risks associated with COVID-19. Given the data so far, the choice is not a Cornelian dilemma. COVID-19 disease has been found to associate with an increased risk to develop abnormal characteristics [12, 16], slightly modified ovarian reserve and reduced number and quality of embryos [16]. The story keeps unfolding on the association between COVID-19 disease and menstrual health, but given the current state of knowledge, for the sake of the health of my own menstrual cycles, I would rather go for the vaccine than face a SARS-CoV-2 infection unvaccinated.

### Declaration of interests

The author has no interests to declare.

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<https://doi.org/10.1016/j.molmed.2023.06.005>

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