



Covid-19 vaccines and menstrual changes

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Continued need for well designed studies

Menstrual irregularities are very common, and affect women's health, wellbeing, and daily life.¹ Before the covid-19 vaccination roll-out, menstrual changes after vaccination were rarely reported to spontaneous reporting systems, and no associations between vaccination and menstrual features had been noted. One study addressing menstrual changes found no increased occurrence in vaccinated girls, but described changes after vaccination in health seeking and reporting behaviour around menstruation.²

Since vaccination for covid-19 was initiated in late December, 2020, unforeseen signals of menstrual changes as possible side effects of the vaccines have been detected by spontaneous reporting systems in many countries. The UK Yellow Card, reporting data up to 24 August 2022, had a total of 51 435 suspected reactions that had been reported after all three covid-19 vaccines, relating to various menstrual disorders (eg, heavier than usual periods, delayed periods, and unexpected vaginal bleeding).³ Commonly, heavy menstrual flow has been reported.⁴ In Sweden, an increase in visits to the doctors for abnormal uterine bleeding and menstrual irregularities have been observed after covid-19 mRNA vaccination in a nationwide, registry-based study.⁵ Importantly, most reported changes have been intermittent and self-limiting, and no causal associations have been established.⁶ Reassuringly, studies have found no indications that covid-19 vaccination changes fecundity or the risk of first-trimester miscarriage.^{7 8}

Nevertheless, compelling data show that men and women differ in their immune responses to viral vaccines.⁹ Moreover, sex affects the frequency and severity of reported adverse effects of vaccination, including fever, pain, and inflammation, likely influenced by genetic and hormonal factors.⁹ Given the novelty and the magnitude of the spontaneously reported menstrual changes after covid-19 vaccination, exploration of the associations of sex specific outcomes to vaccination is imperative. Well designed studies can inform the female population, secure transparency in vaccine safety issues, and maintain public trust in vaccination programmes and surveillance systems. Ultimately, the key question remains: can covid-19 vaccines cause menstrual changes?

Blinded, randomised controlled trials are best fitted to answer this question. Regrettably, women's health issues have been under-represented or excluded from many clinical studies in the past.¹⁰ Information into menstrual changes have not previously been included in randomised controlled

vaccine trials, and are unaddressed in randomised controlled trials to date.

When randomised controlled trials are not feasible, well designed, longitudinal, epidemiological studies are key to gain a better understanding of potential causal effects on adverse events, as advised by the World Health Organization.¹¹ Control of bias is a central component. Combining evidence from different epidemiological approaches with differing sources of bias might improve causal inference if results are consistent. Where results show divergent associations, understanding the key sources of bias can help to direct researchers to what type of research is needed.¹² In the assessment of causality, temporal relation with vaccination, strength of associations, dose-response relation, consistency of evidence across studies, specificity of exposures, and biological plausibility all need thorough evaluation.¹¹

An adverse event after immunisation (AEFI) is defined as any untoward medical occurrence after immunisation but that does not necessarily have a causal association with the vaccine.¹¹ Addressing associations is particularly challenging when the reported AEFI is frequently occurring in the population regardless of vaccination. A pre-pandemic study of 267 209 US women found that 22% of women aged 18-39 years had cycle irregularities.¹³ In a mass vaccination situation, such as the covid-19 pandemic, menstrual changes will inevitably occur regardless of vaccination, and assessing potential excess risks due to vaccination is challenging. Moreover, people might be more likely to report side effects in response to vaccine safety concerns reported in the media. In such situations, even the absolute criterion for causality, namely that the exposure must occur before the outcome, can be difficult to establish.

In the linked paper by Edelman and colleagues (doi:10.1136/bmjmed-2022-000297), the authors look at menstrual cycle disturbances after covid-19 vaccination in a large, cohort study of prospectively collected data.¹⁴ They used data from almost 20 000 women using the Natural Cycles application between 1 October 2020 and 7 November 2021. This application allows users to record and observe their menstrual cycle and manage their fertility. The authors published a study based on the same application with very similar results in January 2022.¹⁵ However, in the updated analyses, the sample size was increased to include participants from Europe, Canada, USA, Australia, and New Zealand. Moreover, follow-up was extended by two months, and additional vaccine types and dosing schedules were included.

The study sample included women aged 18-45 years who were at least three menstrual cycles after

pregnancy or after hormone contraceptive use, were not menopausal, and had pre-vaccination cycle lengths (24–38 days). A two sided t test was used to compare the mean within-individual change in cycle and menses lengths by vaccination status, and mixed effects models to estimate adjusted differences. Compared with unvaccinated individuals, the first vaccine dose was associated with a mean cycle increase of 0.71 days (99.3% confidence interval 0.47 to 0.96), whereas the second dose was associated with an increase of 0.56 days (0.28 to 0.84). Edelman and colleagues also reported that the average cycle increase was 3.70 days (2.98 to 4.42) for women who received two doses within the same cycle, which might suggest a dose-response association. Other studies have shown that the mean cycle length was increased for women vaccinated during the follicular phase, whereas no change was found if women were vaccinated during the luteal phase.¹⁶ These findings agree with the results of Edelman and colleagues' study because two vaccinations given during one cycle suggest that one was given during the follicular phase. Analyses of menses lengths showed a small but significant mean difference in change of 0.13 days (0.06 to 0.20) after the second dose, however, this result is mainly explained by shorter menses lengths of the women who were not vaccinated.

We commend Edelman and colleagues for this large study where information on menstruation was collected before vaccination and also included individuals who were not vaccinated. Prospective collection of data prevents recall bias, which is a major concern in many existing publications on the topic. Selection bias might still have occurred because consent to participate in research was retrieved retrospectively, and the extent to which users of fertility applications are representative of the general menstruating population is unclear.

Edelman and colleagues' analysis, using mean differences, can describe a change in menstrual cycle if the change moves in one direction (ie, longer or shorter). If irregularities after vaccination comprise a mix of both shorter and longer cycles or menses, as suggested from other studies,¹⁷ no changes or small changes in mean differences do not exclude potential alterations after vaccination. No clear measures of range or variance in cycle or menses length is reported, therefore, firm conclusions are difficult to make about the interval changes after covid-19 vaccination. The findings regarding menses lengths are particularly difficult to interpret because significant estimated results were produced from changes among women who were not vaccinated. Information about the proportion of women who have no changes or different degrees of changes in intervals of menstrual cycles, as well as mean cycle and menses lengths before

vaccination, are key measures that would have aided the interpretation.

This study is based on associations from an observational design, thus, in itself, is insufficient to infer causation. Moreover, the mean menstrual cycle changes were intermittent and self-limiting, although women vaccinated with two doses within the same cycle had a longer duration of changes.

Although further research is needed to conclude findings, the significant mean changes to menstrual cycles observed by Edelman and colleagues suggest that menstrual changes might occur as a result of covid-19 vaccines. Unfortunately, changes in menstrual flow, which have been repeatedly reported, were not looked at in this large prospective study. Potential mechanisms have been suggested by others, spanning from immune related stress on the hypothalamic-pituitary-ovarian axis to local endometrial changes.⁴

There is an important women's health imperative to clarify whether covid-19 vaccines can cause menstrual changes, and more studies are needed. Menstrual changes (and postmenopausal bleedings) should be included in future randomised controlled trials, but well designed cohort studies that include a wider spectrum of changes, and take the co-occurrence of infections into account, can also provide valuable new insights.

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