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## Menstrual changes after covid-19 vaccination

### A link is plausible and should be investigated

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Common side effects of covid-19 vaccination listed by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) include a sore arm, fever, fatigue, and myalgia.<sup>1</sup> Changes to periods and unexpected vaginal bleeding are not listed, but primary care clinicians and those working in reproductive health are increasingly approached by people who have experienced these events shortly after vaccination. More than 30 000 reports of these events had been made to MHRA's yellow card surveillance scheme for adverse drug reactions by 2 September 2021, across all covid-19 vaccines currently offered.<sup>1</sup>

Most people who report a change to their period after vaccination find that it returns to normal the following cycle and, importantly, there is no evidence that covid-19 vaccination adversely affects fertility. In clinical trials, unintended pregnancies occurred at similar rates in vaccinated and unvaccinated groups.<sup>2</sup> In assisted reproduction clinics, fertility measures and pregnancy rates are similar in vaccinated and unvaccinated patients.<sup>3-6</sup>

MHRA states that evaluation of yellow card reports does not support a link between changes to menstrual periods and covid-19 vaccines since the number of reports is low relative to both the number of people vaccinated and the prevalence of menstrual disorders generally.<sup>7</sup> However, the way in which yellow card data are collected makes firm conclusions difficult. Approaches better equipped to compare rates of menstrual variation in vaccinated versus unvaccinated populations are needed, and the US National Institutes of Health has made \$1.67m (£1.2m; €1.4m) available to encourage this important research.<sup>8</sup>

Menstrual changes have been reported after both mRNA and adenovirus vectored covid-19 vaccines,<sup>1</sup> suggesting that, if there is a connection, it is likely to be a result of the immune response to vaccination rather than a specific vaccine component. Vaccination against human papillomavirus (HPV) has also been associated with menstrual changes.<sup>9</sup> Indeed, the menstrual cycle can be affected by immune activation in response to various stimuli, including viral infection: in one study of menstruating women, around a quarter of those infected with SARS-CoV-2 experienced menstrual disruption.<sup>10</sup>

Biologically plausible mechanisms linking immune stimulation with menstrual changes include immunological influences on the hormones driving the menstrual cycle<sup>11</sup> or effects mediated by immune cells in the lining of the uterus, which are involved in the cyclical build-up and breakdown of this tissue.<sup>12</sup> Research exploring a possible association

between covid-19 vaccines and menstrual changes may also help understand the mechanism.

Although reported changes to the menstrual cycle after vaccination are short lived, robust research into this possible adverse reaction remains critical to the overall success of the vaccination programme. Vaccine hesitancy among young women is largely driven by false claims that covid-19 vaccines could harm their chances of future pregnancy.<sup>13</sup> Failing to thoroughly investigate reports of menstrual changes after vaccination is likely to fuel these fears. If a link between vaccination and menstrual changes is confirmed, this information will allow people to plan for potentially altered cycles. Clear and trusted information is particularly important for those who rely on being able to predict their menstrual cycles to either achieve or avoid pregnancy.

We are still awaiting definitive evidence, but in the interim how should clinicians counsel those who have experienced these effects? Initially, they should be encouraged to report any changes to periods or unexpected vaginal bleeding to the MHRA's yellow card scheme. This will provide more complete data to facilitate research into any link and signal to patients that their concerns about vaccine safety are taken seriously, building trust. In terms of management, the Royal College of Obstetricians and Gynaecologists and the MHRA recommend that anyone reporting a change in periods persisting over several cycles, or new vaginal bleeding after the menopause, should be managed according to the usual clinical guidelines for these conditions.<sup>7-14</sup>

One important lesson is that the effects of medical interventions on menstruation should not be an afterthought in future research. Clinical trials provide the ideal setting in which to differentiate between menstrual changes caused by interventions from those that occur anyway, but participants are unlikely to report changes to periods unless specifically asked. Information about menstrual cycles and other vaginal bleeding should be actively solicited in future clinical trials, including trials of covid-19 vaccines.

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