

Norwegian Institute of Public Health, Division of Infection Control, Case number 1

Institution: Norwegian Institute of Public Health
Administrative unit: Division of Infection Control
Title of case study: COVID-19 vaccines and menstrual disturbances
Period when the underpinning research was undertaken: 2020-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2023
Period when the impact occurred: 2022-2023

1. Summary of the impact (indicative maximum 100 words)

Menstrual irregularities are very common, and affect women's health, wellbeing, and daily life. Following the launch of the covid-19 vaccination campaign, signals of heavy menstrual bleedings were reported. We took advantage of existing population-based cohorts and confirmed positive associations between COVID-19 vaccination and heavy menstrual bleeding in different age groups. The findings were part of the evidence evaluated by the European Medicines Agency, which resulted in the recommendation that heavy menstrual bleeding should be added to the mRNA vaccines' product information as a side effect of unknown frequency.

2. Underpinning research (indicative maximum 500 words)

Menstrual irregularities are very common, and affect women's health, wellbeing, and daily life. Before the covid-19 vaccination roll-out, menstrual changes after vaccination had rarely been reported to spontaneous reporting systems for adverse events following immunization (AEFIs), and no associations between vaccination and menstrual features had been noted. After the initiation of the covid-19 vaccination campaigns, unforeseen signals of menstrual changes as possible side effects of the vaccines were detected by spontaneous reporting systems in many countries, including Norway.

The first research effort was to explore the potential association between covid-19 vaccination and menstrual disturbances in 18-30 year old women, using population-based questionnaire data from 3972 cohort participants (YoungAdult cohort, see below).¹ The prevalence of any menstrual disturbance was high: 36.7% in the last menstrual cycle *prior* to the first vaccine dose. We observed increased risk of heavier menstrual bleeding than usual in the first cycle after the first vaccine dose as compared to the last cycle prior to vaccination, RR = 1.90 (95 % CI: 1.69-2.13). Increased risks were also observed for prolonged bleeding, shorter interval between menstruations, and stronger period pain. The results were unaffected by vaccine brand, contraception/hormone use, or presence of existing gynecological condition(s), and were similar in women who were tracking their menstruation using an app or other method.

The second research effort was to explore the association between vaccination and menstrual disturbances in 7 565 adolescent girls aged 12-15 years using maternal questionnaire responses in a large population-based cohort (MoBa, see below).² Menstrual irregularities were common also in this age group, independent of vaccination and infection status. The proportion of vaccinated girls reporting one or more menstrual irregularities in their last period *prior* to vaccination was 22.6%, while 25.1% of this group reported at least one event for the first cycle *after* vaccination. Unusually heavy bleeding was reported by 4.7% prior to vaccination and 7.3% after vaccination, RR = 1.61 (95 % CI 1.43 to 1.81). The effect sizes were similar in girls who were tracking their menstruation using an app or other method.

The third effort aimed at exploring the risk of unexpected vaginal bleeding in women who were not menstruating due to hormone use or menopause. Through electronic questionnaires issued

during the pandemic, a total of 22,000 women in a cohort of Seniors (see below) and the Norwegian Mother, Father and Child Study (MoBa) were asked if they had experienced unexpected vaginal bleeding in 2021, the year when the vast majority received their first COVID-19 vaccine dose.³ Among the women who reported of such bleeding, close to 50% stated that the change had occurred within four weeks of COVID-19 vaccination. Across all three groups of women, we found an 2-4 times increased risk of unexpected vaginal bleeding in the first month following vaccination.

Key researchers (from the research unit SMHB):

Kristine Blix, Researcher (15.03.2022-today)
 Berit Feiring, Senior Adviser (01.03.1989-today)
 Ida Laake, Senior Researcher (05.08.2013 – today)
 Anna H Robertson, Senior Adviser (01.09.2013-today)
 Siri Mjaaland, Senior Researcher (-1.10.2007-today)
 Lill Trogstad, Head of Section (13.07.2009-today)

3. References to the research (indicative maximum of six references)

1. **Trogstad L, Laake I, Robertson AH, Mjaaland S, Caspersen IH, Juvet LK, Magnus P, Blix K, Feiring B.** Heavy bleeding and other menstrual disturbances in young women after COVID-19 vaccination. *Vaccine*. 2023 Aug 14;41(36):5271-5282. doi: 10.1016/j.vaccine.2023.06.088. Epub 2023 Jul 3. PMID: 37451876. <https://pubmed.ncbi.nlm.nih.gov/37451876/>
2. **Trogstad, Lill.** Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination (January 1, 2022). Available at SSRN: <https://ssrn.com/abstract=3998180> or <http://dx.doi.org/10.2139/ssrn.3998180> Preprint
3. **Blix K, Laake I, Juvet L, Robertson AH, Caspersen IH, Mjaaland S, Skodvin SN, Magnus P, Feiring B, Trogstad L.** Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. *Sci Adv*. 2023 Sep 22;9(38):eadg1391. doi: 10.1126/sciadv.adg1391. Epub 2023 Sep 22. PMID: 37738335; PMCID: PMC10516485 <https://pubmed.ncbi.nlm.nih.gov/37738335/>
4. Caspersen IH, Juvet LK, **Feiring B, Laake I, Robertson AH, Mjaaland S, Magnus P, Trogstad L.** Menstrual disturbances in 12- to 15-year-old girls after one dose of COVID-19 Comirnaty vaccine: Population-based cohort study in Norway. *Vaccine*. 2023 Jan 9;41(2):614-620. doi: 10.1016/j.vaccine.2022.11.068. Epub 2022 Dec 2. PMID: 36517325; PMCID: PMC9715483. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9715483/>
5. **Trogstad L, Juvet L, Feiring B, Blix K.** Covid-19 vaccines and menstrual changes. *BMJ Med*. 2022 Oct 21;1(1):e000357. doi: 10.1136/bmjmed-2022-000357. PMID: 36936587; PMCID: PMC9951358. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9951358/>

4. Details of the impact (indicative maximum 750 words)

Since March 2020, biweekly questionnaires were issued to participants in two already ongoing population based cohort studies at the NIPH, namely The Norwegian mother, father and child study (MoBa, <https://www.fhi.no/en/ch/studies/moba/>) and the Norwegian Influenza Cohort Study (NorFlu, <https://www.fhi.no/en/id/studies/norflu/>). The MoBa and NorFlu cohorts are pregnancy cohorts and have followed parents and children since pregnancy in 1998 and 2009, respectively. During the SARS-CoV-2 pandemic, a YoungAdult cohort (ages 18-30, <https://www.fhi.no/en/id/corona/studies/ungvoksen/>) and a Senior cohort (ages 65-80, <https://www.fhi.no/en/id/corona/studies/the-senior-cohort/>) were recruited to provide data for age groups not covered in the MoBa/NorFlu. Similar questionnaires were issued in all cohorts and linked to individual, national registry data on SARS-CoV-2 vaccination and infection. The overall objective is to understand the course and consequences of health crises like pandemics, encompassing short- and long-term consequences of infections and vaccination: We monitor

vaccine effectiveness, immune responses and adverse reactions, and the course of SARS-CoV-2 infection. The results are applied in public advice and decision-making, with emphasis on optimized vaccination strategies, and published scientifically.

The specific research initiative on menstrual disturbances following COVID-19 vaccination started in spring of 2021, after the launch of the COVID-19 vaccination campaign in Norway in late December of 2020. In the questionnaire free-text fields, many participants noted that they experienced heavy menstrual bleeding following vaccination. This led us to include structured questions on unexpected vaginal bleeding and menstrual disturbances in questionnaires to female participants. During the summer of 2021, the Norwegian Medicines Agency, NMA received many reports of heavy menstrual bleeding after COVID-19 vaccination.

Preliminary results from the cohort analyses were shared in confidentiality with the NMA. Based on these results and the high number of spontaneously reported bleeding episodes, the NMA decided to report heavy menstrual bleeding as a potential side effect of COVID-19 vaccines to the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA).

The cohort studies among 12-15- year- old adolescents and 18-30- year- old women were referred to the EU regulatory network (EMA and the national competent authorities in the EU/EEA countries) by the Norwegian PRAC Rapporteur, for discussion in PRAC's June 7-10 plenary, 2022. On May 23, 2022, Lill Trogstad was contacted by the Signal Management Lead at the Pharmacovigilance Office of EMA, Irina Caplanusi, and asked to present the preliminary study results at the PRAC June plenary meeting under a confidentiality commitment. The presentation to PRAC was held on June 7, 2022.

On October 27, 2022, the PRAC recommended to include "heavy menstrual bleeding" as a side effect of unknown frequency to Spikevax.^{4,5} On November 10, 2022, the PRAC Committee recommended that heavy menstrual bleeding should be added also to the Comirnaty product information as a side effect of unknown frequency.⁶ The publications and the recommendations from PRAC/EMA received much media attention. In Norway, 128 media articles were published in 2021- 2023. The preprint publication that was available at this time received more than 20 000 views/downloads, 4 international policy citations and 19 international news stories.⁷

Post menopausal bleeding has also been reported following COVID-19 vaccination. Our third publication, on unexpected vaginal bleeding in non-menstruating women, has been referred to EMA by the NMA for the current evaluation of post-menopausal bleeding as a side effect to COVID-19 vaccination. This paper is in the top 5% of all research outputs scored by Altmetric and was viewed/downloaded more than 53 000 times the first 30 days after publication, and a total 40 news stories from 27 outlets are listed.⁸

Given the novelty and the magnitude of the spontaneously reported menstrual changes after COVID-19 vaccination, exploration of the associations of sex-specific outcomes after vaccination is imperative. Well-designed studies can inform the female population, secure transparency in vaccine safety issues, and contribute to maintaining public trust in vaccination programmes and surveillance systems. Blinded, randomised controlled trials are best suited to address this issue. However, menstrual changes are unaddressed in such trials to date.

A mass-vaccination setting with such high coverage and rapid roll-out, leaves limited opportunity to retrospectively compare the frequency of adverse events in vaccinated and unvaccinated individuals. While severe reactions can be captured by health registries, non-severe outcomes may go undetected without active real-time monitoring. We have demonstrated that dynamic data

collection within existing cohorts is a powerful tool in gaining timely, new insights during an ongoing health crisis.

6. Sources to corroborate the impact (indicative maximum of ten references)

¹<https://www.fhi.no/en/id/corona/studies/ungvoksen/increased-incidence-of-menstrual-changes-among-young-women/>

²<https://www.fhi.no/en/news/2022/increased-incidence-of-menstrual-disturbances-after-coronavirus-vaccination/>

³<https://www.fhi.no/en/news/2023/vaginal-bleeding-after-covid-19-vaccination-among-non-menstruating-women/>

⁴https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-heavy-menstrual-bleeding-covid-19-mrna-vaccine-spikevax_en.pdf

⁵https://www.ema.europa.eu/en/documents/prac-recommendation/new-product-information-wording-extracts-prac-recommendations-signals-adopted-24-27-october-2022-prac-meeting_en.pdf

⁶https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccines-safety-update-10-november-2022_en.pdf

⁷https://plu.mx/ssrn/a/?ssrn_id=3998180 ⁸

⁸<https://scienceadvances.altmetric.com/details/154536038>

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