The effect of the vaccine for COVID-19 on menstrual cycle symptoms in healthy women

Protocol Number 1
Version: 0.2
Date: 24/09/2021

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Sponsor/s: Nil

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

STUDY SYNOPSIS

Title:	The effect of the vaccine for COVID-19 on menstrual cycle symptoms in healthy women
Design:	Prospective
Recruitment sites:	Vaccination hubs, GP vaccination clinics, vaccinating pharmacies, social media
Study Question:	Does the COVID vaccine alter menstrual pattern?
Primary Objectives:	Define the frequency of changes to the menstrual cycle patterns in women of reproductive age following the vaccine for COVID-19
Secondary Objectives:	1. To compare the change in bleeding volume for each participant before and after the vaccination. 2. To compare the change in bleeding length for each participant before and after the vaccination. 3. To compare the change in bleeding regularity for each participant before and after the vaccination. 4. To compare the change in dysmenorrhoea NRS score for each participant before and after the vaccination. 5. To asses the duration of the above changes
Subgroups:	Pfizer vaccinated participants. Astra Zeneca vaccinated participants. Moderna vaccinated participants.
Inclusion Criteria:	• Premenopausal individuals who have had at least one period in the past • Currently having periods or • Currently not having periods due to other reasons eg. using hormonal contraceptives, using gender affirming hormones • Have not yet been vaccinated but are planning on having the COVID-19 vaccine soon or have received their first dose on day of recruitment • Healthy people (without blood disorders or known hematological diseases) • Aged 18-45 • Interested in participating in the study and consent to regular monitoring of their menstruation.
Exclusion Criteria:	• People who are already vaccinated against COVID • People who never had periods • People who are post menopausal, pregnant, breastfeeding or

	who plan pregnancy in the next 12 months. • People who have had a hysterectomy
Number of Planned Subjects:	1200 - 600 for each vaccine

Glossary of Abbreviations & Terms

Abbreviation	Description (using lay language)
COVID-19	coronavirus disease
NRS	numeric rating score

Introduction:

Recently in countries that have vaccinated large volumes of their population, there have been many reports of women on social media and in other media describing changes in the menstrual cycle after receiving the Pfizer-BioNTech and Astra_Zeneca vaccines for COVID-19. The changes reported include alterations in the pattern of bleeding, postponement or advancement of the menstrual period, intermenstrual spotting, prolongation of bleeding and increased menstrual bleeding (1,2,3,4,5).

Certain vaccines can cause a physiological trigger and increase cortisol levels in the body (6) and thus can cause a temporary change in the menstrual cycle. A state of stress (conscription, war, significant life event) (7,8,9) may directly impact on the menstrual cycle. Furthermore, the inflammatory response induced by a vaccine results in immune system products including cytokines and interleukins which also can have transient actions on the endometrium.

In addition, the vaccine may affect menstrual symptoms such as dysmenorrhea, in other ways, via cytokines and other immune-mediated messengers (10).

Study question: does the vaccine for COVID-19 alter menstrual bleeding patterns in reproductive age women?

Objective: To examine the effect of the vaccine for COVID-19 on the menstrual cycle pattern in women of reproductive age by assesing the following parameters:

1. To compare the change in bleeding volume for each participant before and after the vaccination.
2. To compare the change in bleeding length for each participant before and after the vaccination.
3. To compare the change in bleeding regularity/timing for each participant before and after the vaccination.
4. To compare the change in dysmenorrhoea NRS score for each participant before and after the vaccination.

5. To asses the duration of each of the above changes (up to 12 months).

Menstrual disturbance will be assessed as: menses six or more days earlier or later than expected, intermenstrual bleeding, bleeding length increased or decreased by 2 or more days, and increased amount of bleeding on a 4 point bleeding scale.

Dysmenorrhoea changes - the appearance of new onset or change in dysmenorrhea severity of 2+ points on an 11 point numeric pain scale after vaccination.

Null Hypothesis: The Covid vaccine will cause no change to the pattern of bleeding (duration, volume, intensity, timing) and period related pain in reproductive age women both after a first dose and after two doses.

Participants: This study will involve 1200 people aged 18-45, who will volunteer to perform the study, with each person providing comparator data - comparing the bleeding pattern and pain in the 3 months before receiving the vaccine compared to 3, 6, 9 and again 12 months after receiving the first vaccine.

Criteria for inclusion: The study group will include :

- Premenopausal individuals who have had at least one period in the past
- Currently having periods or
- Currently not having periods due to other reasons eg. using hormonal contraceptives, using gender affirming hormones
- Have not yet been vaccinated but are planning on having the COVID-19 vaccine soon or have had the first dose on the day of recruitment
- Healthy people (without blood disorders or known hematological diseases)
- Aged 18-45
- Who are interested in participating in the study and agree to conducting regular monitoring of their menstruation.

Criteria for exclusion:

- People who are already vaccinated against COVID
- People who never had periods
- People who are post menopausal, pregnant, breastfeeding or who plan pregnancy in the next 12 months.
- People who have had a hysterectomy

Research period: 12 months for data collection.

Sample size: Assuming that at least 20% will report a menstrual change, and a background menstrual irregularity rate of 14% (11), using a 5% significance level and a power of 80%, the required sample size to show a significant increase is 350 for each vaccine. This assumes that the background rate is known rather than estimated from the study. Taking into consideration an estimated over 50% drop-out by the 12 month qestionnaire, we will recruit 600 participants for each vaccine.

Study design: This will be a prospective study. The recruitment of people and their consent to participate in the research will be done in COVID vaccination hubs, GP vaccination clinics, vaccinating pharmacies and via social media. Multiple sites and social media will be used for advertising purposes and they will not be listed on the HREA. Potential recruits will be offered participation by local posters and brochures distributed in the hubs and ads on social media. People will answer a questionnaire that includes personal and medical details and questions regarding menstrual symptoms, the duration and volume of menstrual bleeding during the 3 months prior to receiving the vaccine. A link to the questionnaire which includes the consent process will be provided in the advertisement/brochure and the participants will be able to answer it through their phone while they wait for 15 minutes after their vaccine. The questionnaire is attached.

Additional questionnaires will be sent to the participants through email link 3, 6, 9 and again 12 months after the first vaccine to measure the effect of the vaccine on the menstrual cycle in terms of length, regularity, amount and pain.

All questionnaires will include stress and anxiety assessment in order to try and exclude those effects on the menstrual pattern.

The stress and anxiety questions were taken from validated questionnaires. The bleeding volume assesement and the pain NRS score are validated as well. Other questions were written specifically for this study.

Statistical analysis: The results will be summarized using descriptive statistics and processed using SPSS software. 95% confidence intervals will be calculated for any estimated proportions. Comparisons between proportions will be made using logistic regression. All tests will be two-tailed, and p-value of 0.05 or less and will be considered statistically significant.

Consent: Consent will be undertaken online after the participant has read the background rationale for the study, understanding the commitment, checking the inclusion and exclusion criteria and agreeing to the study requirements.

Participant Safety and Withdrawal:

The discomforts and risks to the participants are minimal.

We recognize that the study questionnaires may cause distress for some participants. We explain the type of questions that are going to be asked at the introduction to the consent: such as regarding stress, anxiety, reproductive history, medical history, menstrual bleeding and pain. This may be uncomfortable for people who have experienced pregnancy loss or may cause discomfort for some queer, trans, and/or non-binary participants. People can choose not to participate at this stage.

If a participant chooses to withdraw after the initial questionnaire, their data will not be included in the study. If they choose to withdraw after one of the post vaccine surveys, then only the data collected upto that stage will be included. If a participant falls pregnant after the initial questionnaire and before a subsequent questionnaire then she will be removed from the study. If a participant falls pregnant after a subsequent questionnaire then she will be removed from the study from that date but her data prior to conceiving will be included in the study.

Possible biases:

Selection bias- People whose menstrual cycle has not changed after receiving the vaccine will report this less and will be less willing to participate compared to people whose menstruation has had some change.

Recall bias - due to the fact that we will recruit people who do not necessarily have regular monitoring of their menstruation, we will request that people that use a menstrual App or diary to track their periods use this recorded information to copy the dates of their periods to our questionnaire.

Data Security & Handling

Details of where records will be kept & How long will they be stored:

The online survey will be administered recorded and stored through REDCap. All computerized information will be kept in a database that is password protected at The Royal Women's Hospital. Only members of the research team will have the password. All information will be kept for a period of 7 years after the project is completed, at which time hard copy records will be shredded and computer files deleted. Only aggregate, de-identified data will be published in scientific papers or reports resulting from this work.

Confidentiality and Security:

Each subject will be provided with a unique study identification number (study ID). Identifiable information that is collected in this study will only be accessible by research staff with security access.

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